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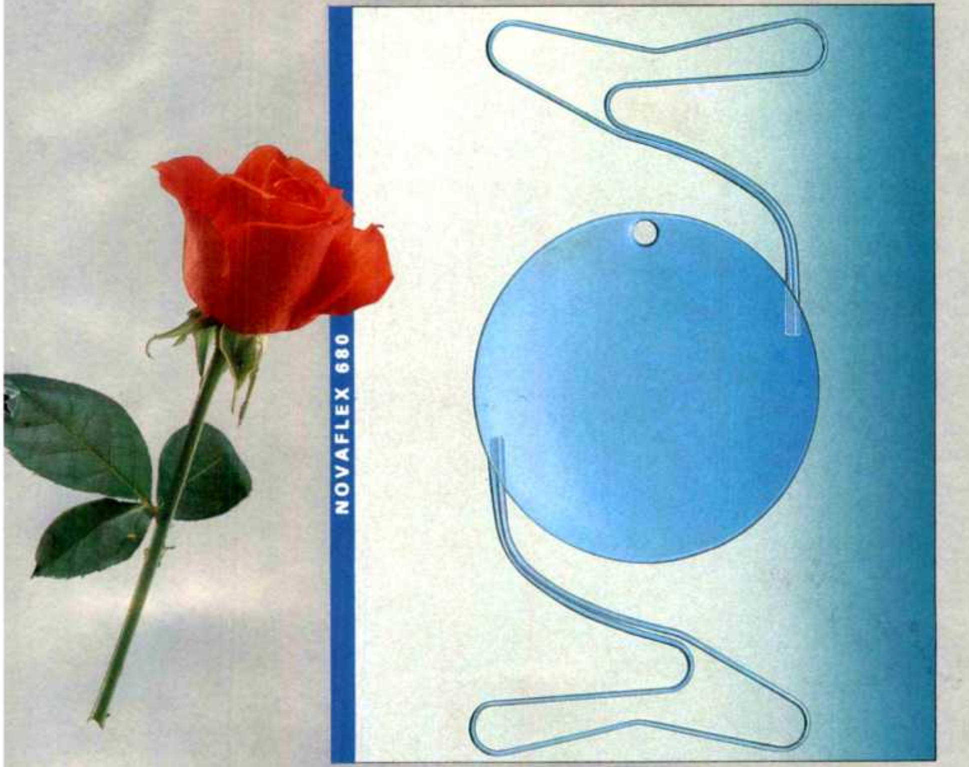

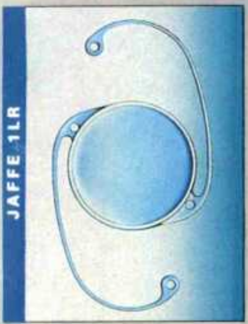

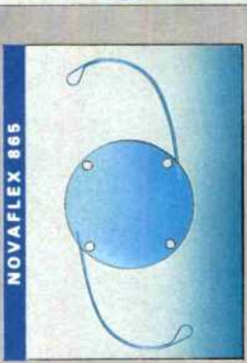

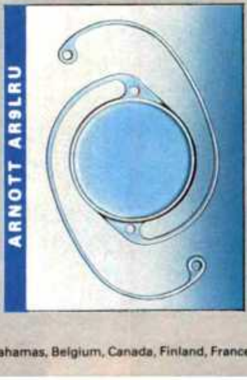

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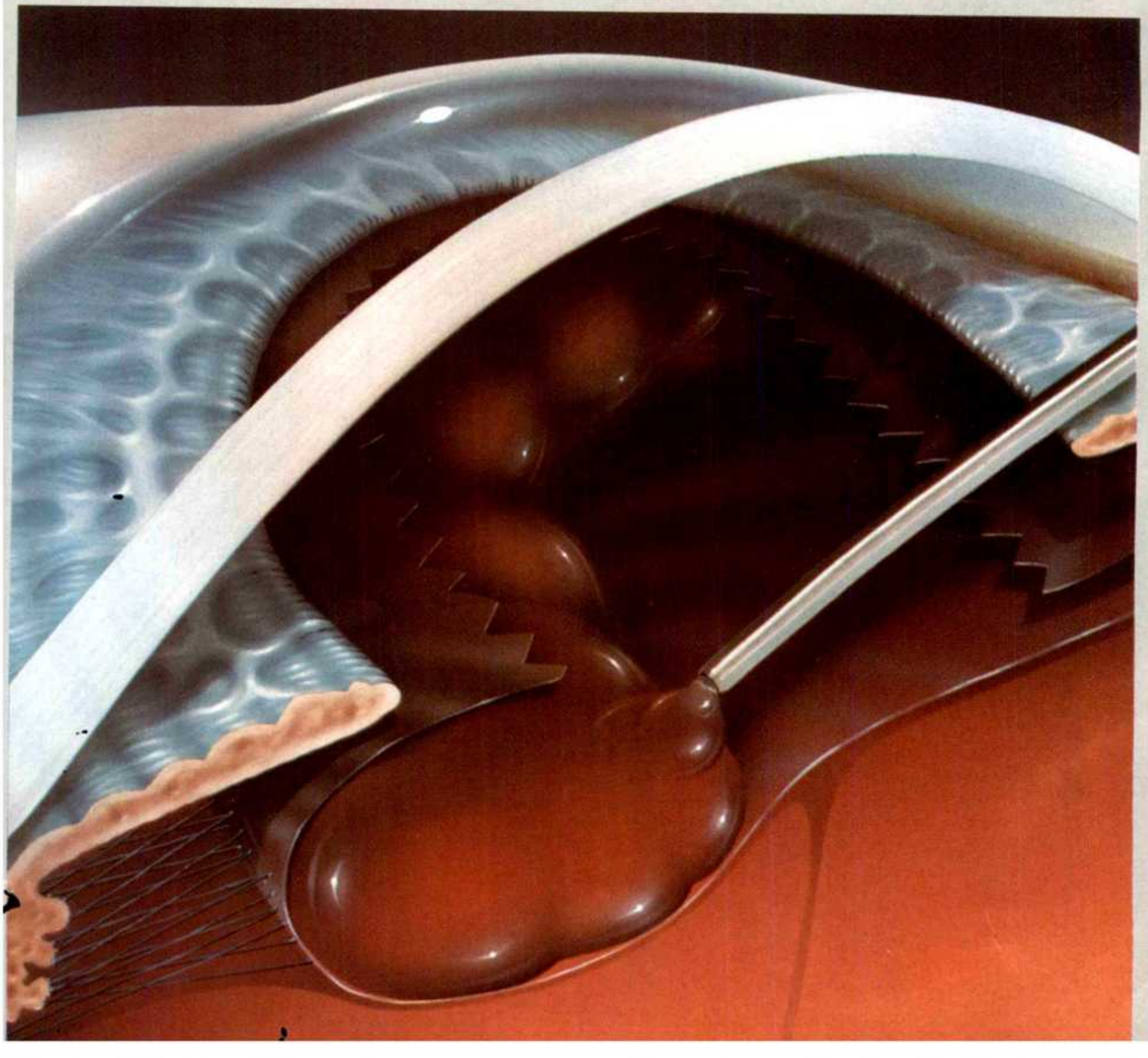

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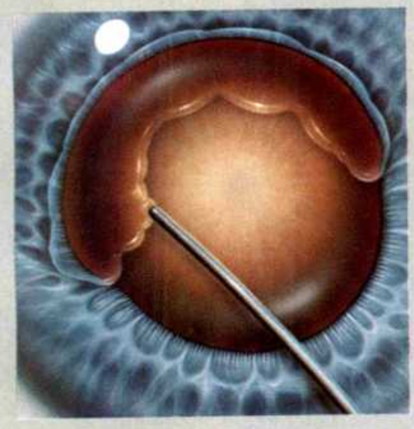

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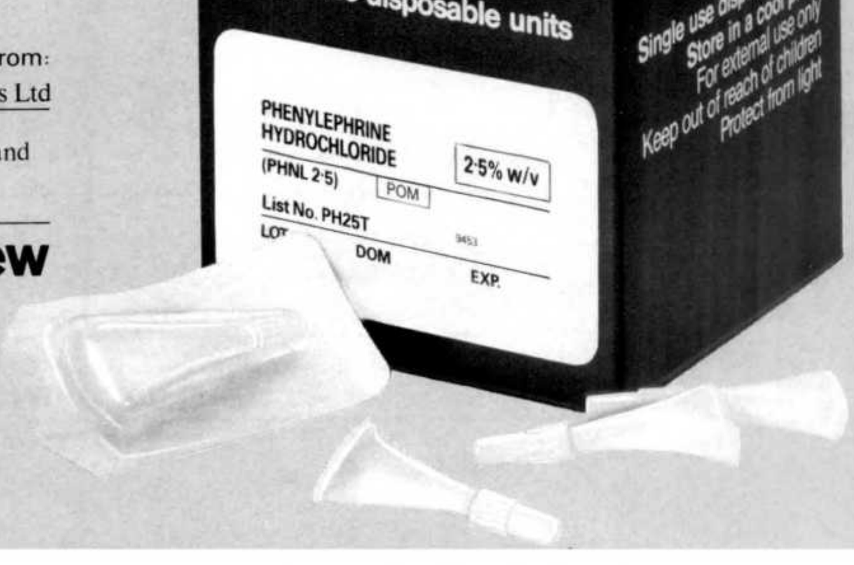

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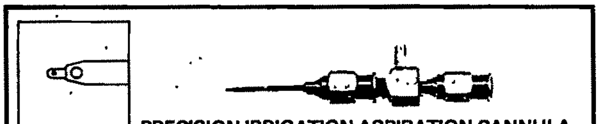

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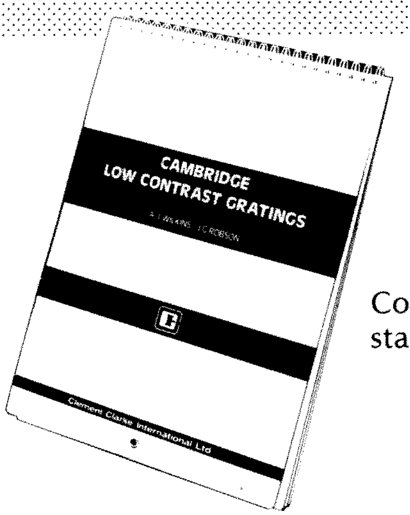

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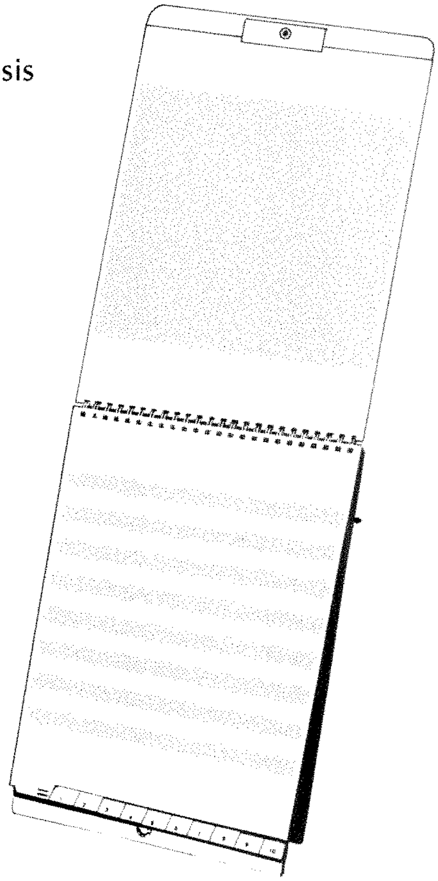

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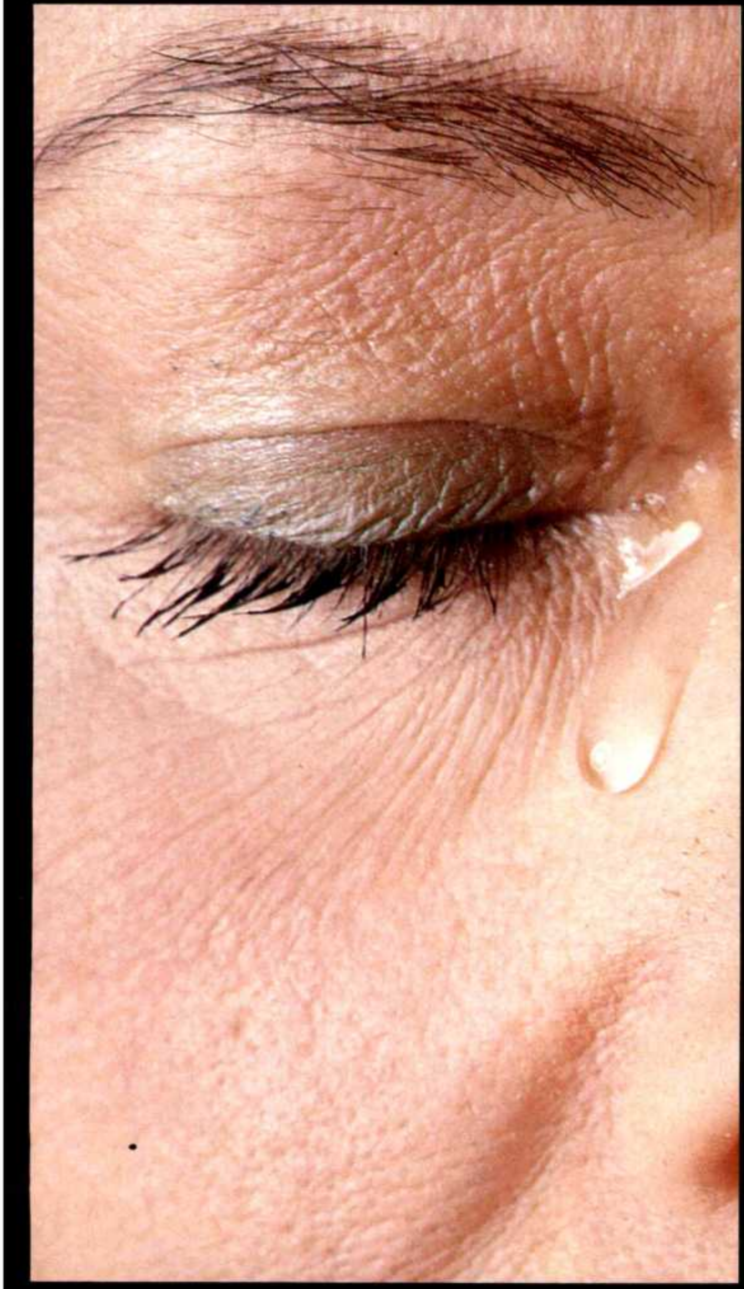

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British Journal of Ophthalmology, 1987, **71**, 1

Editorial: Low dose fluorescein angiography

On naked eye inspection the blood inside vessels does not look as though it is actually moving. Even the very word 'vessel' describes a container meant to hold static fluid, while the word 'vein' can mean a coloured streak such as one sees in marble or geological strata of various colours of rock or minerals.

The speedy flow of the circulation is belied by the perfectly stationary appearance of the blood to an outside observer in, say, a vein on the back of one's hand or in those little red threads one can see in the whites of one's eyes more easily some mornings than others. Twenty-five years ago Novotny and Alvis gave the first demonstration in the retina of the speed and urgency of the circulation of the blood, a phenomenon which most of us had never previously witnessed except in an attenuated form in biology classes in the web of the frog's foot.

Fluorescein angiography of the retina has become an important part of ophthalmology and has demonstrated new pathological mechanisms, given new opportunities for diagnosis, and provided guidance for treatment in the major types of retinal disease. Its success has depended on many factors, one of the most important of which is the impermeability of normal retinal vessels to the fluorescein molecule, allowing a view of the retinal circulation in detail provided the vessel walls are all normal. With other tissues, however, we are not so lucky, as fluorescein escapes from normal connective tissue capillaries. Hence fluorescein angiography of tissues other than the retina has always been more difficult owing to blurring and fogging of the view by early 'leakage.'

Meyer and Watson in a paper in this issue describe an ingenious way of improving the quality of fluorescein pictures of the conjunctiva and episclera. They have discovered that if a small dose of fluorescein is used most of it becomes ionically bound to circulating albumin, and this effectively increases the size of the molecules, thus minimising 'leakage.' Photography with sensitive film (to allow for the small quantity of fluorescein in the circulation) then gives pictures of better quality than has been possible hitherto.

Such a device would probably minimise leakage even in pathological vessels so that the technique might be counterproductive in the study of disease, but it comes into its own in the study of normal anatomy, as the present paper shows.

To workers intent on unravelling the mysteries of the circulation in the anterior segment the old familiar diagram of the circulation after Leber must have seemed an inadequate description of the anatomy and flow pathways. The circulation as described by Meyer and Watson seems quite complicated and subject to individual and even intraindividual variation. For example, the anterior episcleral arterial circle seems to supply four different circulations, and yet all these four areas—episcleral, anterior conjunctival, limbal, and iris—can in their turn receive supplies from other deeper vessels. Leakage began to occur between 4 and 10 seconds after 'first flush' and was confined to conjunctival and episcleral capillaries, but there was minimal masking of detail in the early stages.

There can be little doubt that this advance in fluorescein technique will yield further information as it is more widely practised. The authors are to be congratulated for simplifying anterior segment fluorography and they will be forgiven for showing the circulation to be more complicated than it was previously thought to be.

RJHS

British Journal of Ophthalmology, 1987, 71, 2–10

Low dose fluorescein angiography of the conjunctiva and episclera

PAUL A R MEYER AND PETER G WATSON

From the Department of Ophthalmology, Addenbrooke's Hospital, Cambridge

SUMMARY By reducing the dose of injected fluorescein its leakage from conjunctival and episcleral capillaries has been minimised. These vessels have been demonstrated with great clarity, and the venous circulation, previously obscured by extravascular fluorescein, has also been revealed. The anatomy of the anterior segment vessels, and the blood flow within them, has been studied in eight normal subjects. The anterior ciliary arteries feed an anterior episcleral arterial circle that has superficial and deep components. This supplies the anterior conjunctival and episcleral circulations, the limbal arcades, and the iris arterioles. Where the superficial arterial circle is deficient, isolated vessels emerge from the deep segments of the circle to supply the episcleral plexus and conjunctival arterioles. Watershed zones between the anterior and posterior territories of the conjunctival and episcleral circulations overlap. They may fluoresce up to 30 seconds after the anterior ciliary arteries. The scope of this technique and the implications of these findings are discussed.

From its introduction in 1961 fluorescein angiography rapidly became a valuable tool for examining the retinal microcirculation.[1 2] After intravenous injection of sodium fluorescein, the retinal vessels are demonstrated in crisp contrast against a non-fluorescent background. The low molecular weight of sodium fluorescein (376·3 daltons), makes this an ideal probe with which to test the integrity of tight junctions between retinal capillary endothelial cells and between cells of the retinal pigment epithelium, as well as the permeability of Bruch's membrane.

The application of fluorescein angiography to the examination of the anterior segment of the eye was introduced for the limited purpose of demonstrating abnormalities in the iris capillaries, in which endothelial cells are joined by tight junctions.[3-6]

However, the demonstration of episcleral and conjunctival vessels has always been a problem[7 8] because these capillaries leak molecules smaller than serum albumin. The low molecular weight fluorescein rapidly extravasates, obliterating the angiogram, often before the venous phase has been reached.[8 9] This restricts the diagnostic value of such angiograms to the demonstration of early leakage or gross hypoperfusion.[10] The low molecular weight of fluorescein, of such assistance when interpreting retinal angiograms, is therefore a major obstacle during conjunctival and episcleral angiography.

If leakage is to be prevented, all the fluorescein must be associated with large molecules during its passage through the conjunctival and episcleral capillary beds. Sodium fluorescein does bind ionically to circulating albumin, though there is a wide variation between subjects, and approximately 10% remains free at steady state.[11] This is likely to be far higher during the first pass of an injected bolus unless the fluorescein has mixed with an adequate volume of blood before reaching the target capillary bed. The time that mixing takes is directly related to the dose given. This is therefore critical, but sufficiently low doses are usually inadequate to obtain a satisfactory photographic record. However, by using sensitive photographic emulsion, and enhancing its ASA rating during development, such low doses of fluorescein can yield a good image.

Despite the presence of excellent descriptions of the circulations of the anterior segment[12-16] the flow patterns within these vessels are still disputed.[15 17-19] In addition there is still no complete account of the filling and emptying of conjunctival and episcleral capillary plexuses, so vital to our understanding of episcleritis and scleritis.

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Material and methods

SUBJECTS

Eight normal subjects (six males and two females) between the ages of 20 and 35 years participated. None was aware of having suffered from any serious systemic or eye disease, and apart from the contraceptive pill none was taking any medication. All gave their informed consent.

The temporal limbus was studied by a single angiogram in every subject, and four received an additional angiogram of the nasal limbus. To demonstrate consistency of the flow pattern one volunteer underwent three identical studies of the temporal limbus.

ANGIOGRAPHY TECHNIQUE

Each study was preceded by a sequence of colour photographs of the target area (Kodak Ektachrome, 200 ASA), taken on a Zeiss photo-slit lamp at ×6, ×10, and ×16 magnification.

The photo-slit lamp was modified for fluorescein angiography by the addition of a xenon flash unit for off-axis illumination. The excitation filter permitted a waveband of 420–495 nm, and the T50 of the long-pass barrier filter was 515 nm. The flash generator was set to discharge 720 watts at 1·5 or 2-second intervals. The camera was mounted on a 50:50 beam splitter, and photography was performed through an open aperture (f 14) using 400 ASA monochrome film (Kodak Tri-X). The magnification designated on the slit lamp was ×16, giving a magnification factor of 3·5 at the camera back.

0·6 ml of 20% sodium fluorescein (120 mg) was injected very rapidly into an antecubital vein and the photographic sequence of 30 frames began 5 seconds later.

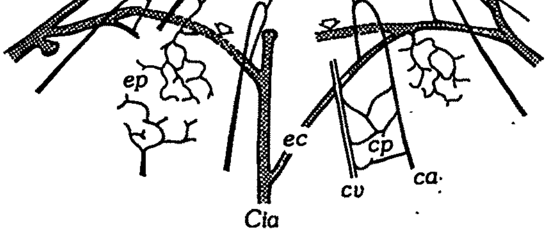

Fig. 1 *Diagrammatic representation of the arterial circulations of the episclera and conjunctive:* Cia=*anterior ciliary artery.* ec=*anterior episcleral arterial circle (deep component marked* ◊*).* ca=*conjunctival arteriole.* ep=*episcleral capillary plexus.* cp=*conjunctival capillary plexus.* la=*limbal arcades.* cv=*conjunctival vein.*

PHOTOGRAPHIC DEVELOPMENT

Each film was processed separately in a developing tank. The developer (Patterson Acuspeed) was diluted and filtered immediately before use. Development proceeded for 9 minutes at 20°C, followed by conventional fixation and washing.

Results

All the angiograms clearly demonstrated the anterior ciliary vessels and the arterial, capillary, and venous phases of the conjunctival and episcleral angiograms. The peripheral iris circulation was also recorded in six of the studies.

The angiographic results were considered together in order to derive common patterns of perfusion. It is these (Fig. 1) that are presented below. With the exception of the timing of the angiographic sequence no quantification of the results was attempted.

NORMAL ANTERIOR SEGMENT FLUORESCEIN ANGIOGRAM:

ARTERIAL PHASE

The positions of the anterior ciliary arteries are inconstant as they run radially towards the limbus within Tenon's capsule. During their course over the anterior part of the globe they usually branch little, if at all.

Close to the limbus they give rise to superficial (anterior episcleral) and deep (scleral) divisions (Figs. 1, 5). The former continue in the superficial or deeper episclera. The latter penetrate the sclera and disappear from view (Fig. 5). In our subjects the scleral contributions were more prominent nasally and the episcleral divisions temporally.

Anterior episcleral arterial circle. The anterior episcleral divisions arise between 1 and 5 mm behind the limbus (Figs. 2, 5). They run forward and circumferentially to anastomose with contributions from the adjacent anterior ciliary arteries, so forming a fragmentary episcleral arterial circle (Fig. 2). The anastomotic vessels may be superficial (Fig. 2) or deep (Fig. 3). The fluorescence from deep vessels is hazy and indistinct (Figs. 2, 3). Superficial episcleral vessels may run deeper at their anastomoses (Fig. 3) and occasionally they dip out of view.

From the anterior episcleral arterial circle four distinct circulations are supplied: episcleral, anterior conjunctival, limbal, and iris.

Episcleral circulation. The episcleral plexus is fed anteriorly from the episcleral arterial circle (Fig. 3) and receives a posterior blood supply from vessels that appear at the level of the muscle insertions. However, areas of episcleral plexus that lie far from an anterior ciliary artery are usually perfused entirely from the episcleral arterial circle (Fig. 4).

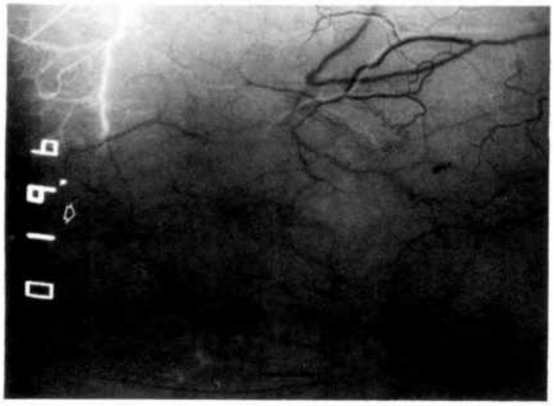

Fig. 2a

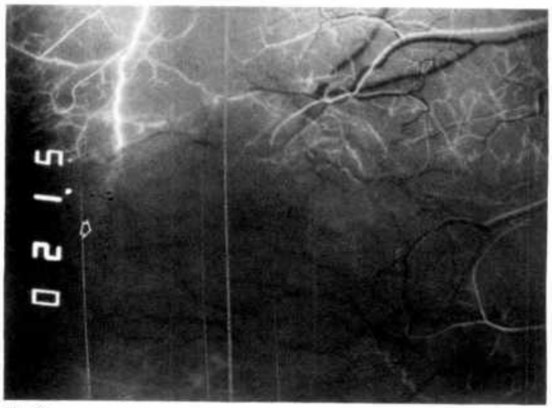

Fig. 2b

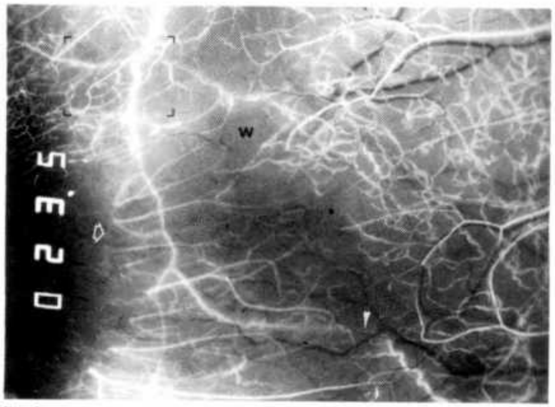

Fig. 2c

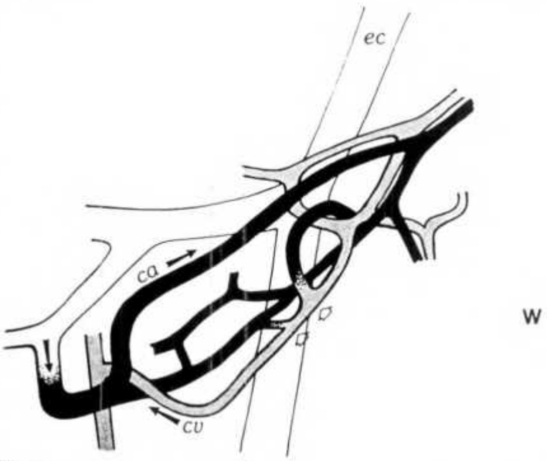

Fig. 2d

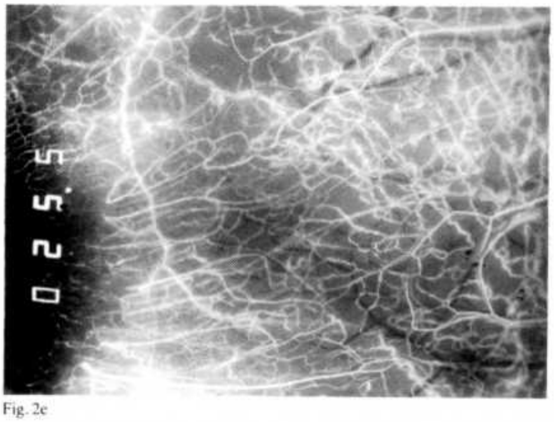

Fig. 2e

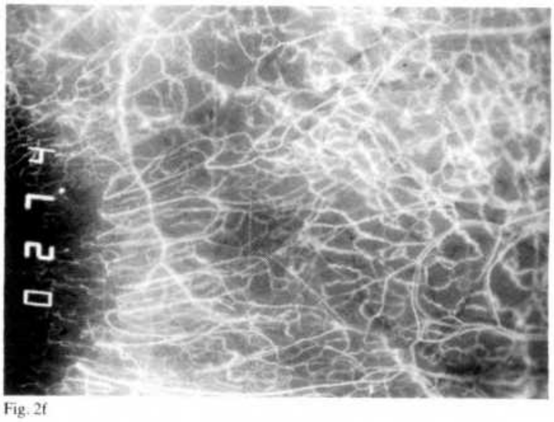

Fig. 2f

Fig. 2 *Left temporal angiogram of a normal 32-year-old female. The time after injection is recorded on each frame. (Scale=1 mm).* (2a) *Fluorescein is first seen in an anterior ciliary artery branch that forms part of the anterior episcleral arterial circle.* (2b) *After supplying a small territory of anterior conjunctiva this vessel penetrates the sclera and continues at a deeper level (⇕; see also Fig. 2c). The posterior tarsal circulation begins to fill. (2c) This fragment of the anterior episcleral arterial circle is completed by a superficial vessel that runs from the point of scleral penetration to an adjacent anterior ciliary artery. The vessel runs deep at (▼). From the episcleral arterial circle anterior roots pass forwards to the limbal reflection of the conjunctiva, where they feed the limbal arcades. They then loop back to supply a rim of anterior conjunctiva. Note the characteristic, irregular net of episcleral capillaries, over which is arrayed the lace-like conjunctival plexus. The watershed zone* (W) *between anterior conjunctival and posterior tarsal contributions to the conjunctival plexus lies about 3 mm from the limbus. This overlies the region of late perfusion of the episcleral plexus.* (2d) *Diagrammatic details of the area bracketed in Fig. 2c. Blood from the episcleral arterial circle* (ec) *is distributed to an anterior root, and thence into conjunctival arterioles* (ca). *Shunting of blood (⇔) from an arteriole into an adjacent conjunctival venule* (cv) *explains the early perfusion of anterior conjunctival venules and the delayed fluorescence of the watershed zone* (W). ec=*anterior episcleral arterial circle.* ca=*conjunctival arteriole.* cv=*conjunctival venule.* (2c, f) *Many radial anterior conjunctival vessels are veins and in the posterior tarsal circulation veins accompany arteries. Leakage of fluorescein is minimal and never obscures anatomical detail.*

The small vessels that supply the episcleral plexus may arise as posterior branches from either the superficial or the deep contributions to the anterior episcleral arterial circle (Fig. 3). Where neither a superficial nor a deep component of the episcleral arterial circle can be seen, the episcleral plexus fills slowly from isolated vessels that emerge from the sclera close to the limbus (Fig. 4). These fluoresce very shortly after the visible episcleral circle. They are identical to episcleral branches from the deeper sections of the visible episcleral arterial circle that can be found in other subjects (Fig. 3).

Anterior conjunctival arterioles. Throughout their superficial course the arteries composing the episcleral circle give rise to fine loops that run forwards into the limbal reflection of the conjunctiva before curving back radially to feed the lacework of the anterior conjunctival capillary plexus (Fig. 2). The delicate column of blood within the anterior conjunctival loops may be punctuated by a string of individual erythrocytes, suggesting that the lumen is in the order of 12 μm (Figs. 2, 5, 6).

Anterior conjunctival loops may also arise from arterioles that emerge from the sclera (Fig. 5).

The posterior conjunctival circulation, which is derived from the posterior tarsal vessels, fills after the anterior conjunctival circulation temporally, but this sequence is often reversed nasally (Fig. 5). Anterior conjunctival loops sometimes anastomose with arterioles of similar calibre derived from the posterior tarsal circulation (Fig. 6).

Limbal arcades (Figs. 5, 6). These are supplied by anterior branches from the episcleral circle, and their origins are usually shared with those of the anterior conjunctival loops. They may fill very late during a normal angiogram.

Iris vessels. The first flush of fluorescein within the radial arterioles of the iris usually coincides with filling of the anterior episcleral arterial circle (Figs. 3, 4).

CAPILLARY PHASE

Episclera. The episcleral capillaries, though always visible, may be difficult to discern below the more prominent conjunctival circulation. They are most clearly seen when the conjunctival circulation fills late for anatomical or pathological reasons (Figs. 2, 4). Fluorescence slowly spreads between the posterior branches of the episcleral circle to illuminate a delicate capillary network covering the sclera. This net also fills from behind, and the anterior and posterior territories meet at a variable distance behind the limbus—a boundary that can normally be recorded (Fig. 2).

Conjunctiva. Fine capillaries form a web that joins the parallel anterior conjunctival arterioles and venules (Figs. 1, 2). Capillaries closest to the limbus fill first and shunt fluorescein into conjunctival venules before any reaches the distal capillary bed (Fig. 2d). The watershed zone separating the territories supplied by the anterior ciliary and posterior tarsal systems may fluoresce very late.

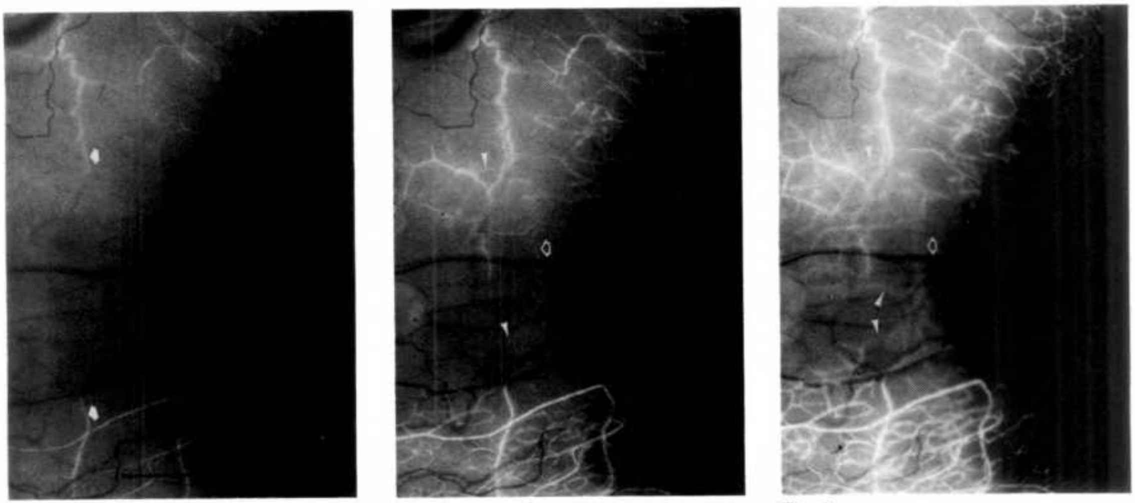

Fig. 3a Fig. 3b Fig. 3c

Fig. 3 *Right temporal angiogram of a normal 23-year-old female.* a: *First flush.* b-c: *Two and four seconds later. (Scale=1 mm). Demonstration of the superficial (♦) and deep (◊) components of the anterior episcleral arterial circle. The episcleral plexus fills from both the superficial and the deep parts of the circle (▼). Note the radial iris arterioles.*

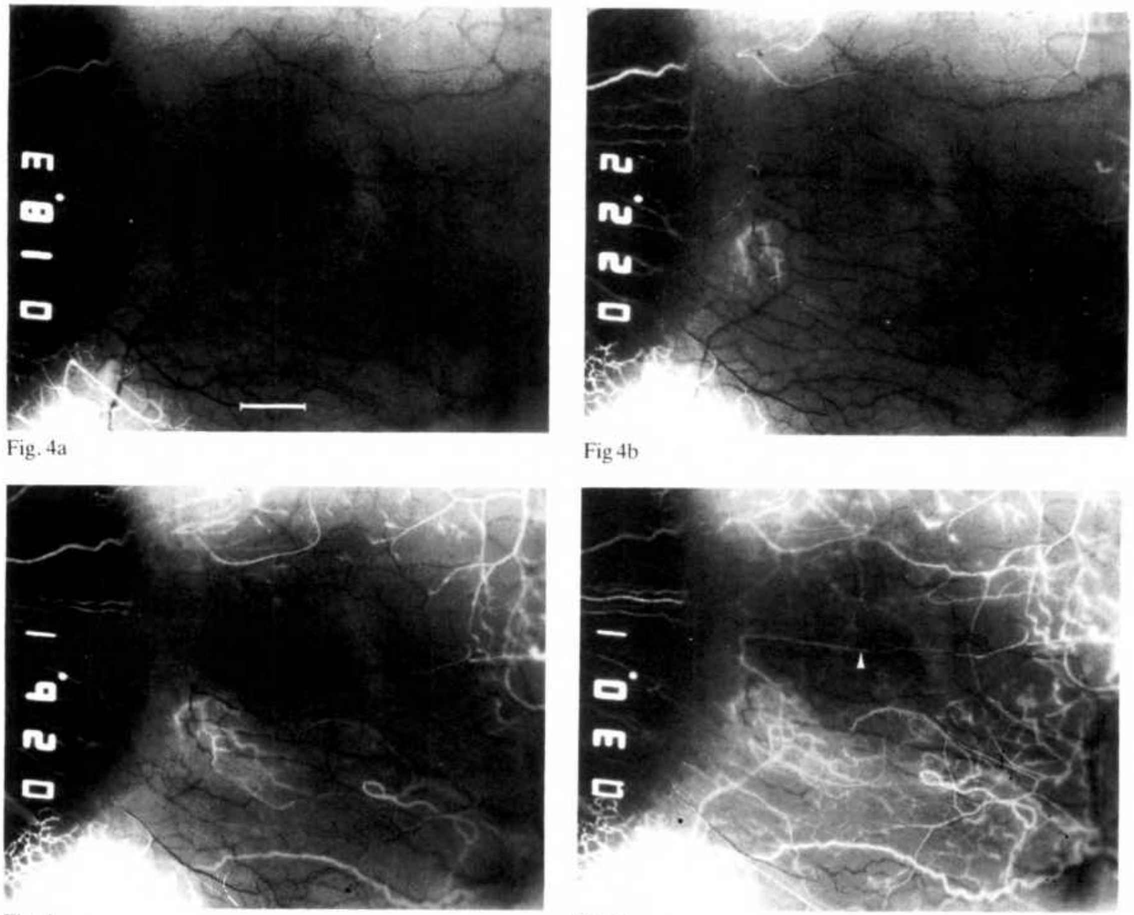

Fig. 4a Fig 4b

Fig. 4c Fig 4d

Fig. 4 *Left temporal angiogram of a normal 34-year-old male. Times after injection recorded on film: first flush was at 16·4 s. (Scale=1 mm). The anterior conjunctival and limbal circulations adjacent to an anterior ciliary artery trunk fill early. The deep component of the anterior episcleral arterial circle and the iris arterioles fluoresce simultaneously. A large expanse of sclera and conjunctiva that is distant from any anterior ciliary artery remains non-perfused until late into the angiogram. The episcleral net in this region is slowly filled from a vessel that emerges from the sclera. This vessel presumably arises from the deep component of the episcleral arterial circle (cf. Fig. 3). An episcleral vein (▲) passes deep to the silhouettes of the anterior conjunctival vessels which are still non-perfused 14 seconds after first flush.*

VENOUS PHASE

Centripetal venules drain the episcleral plexus towards the limbus (Fig. 4) and venules accompany the anterior conjunctival arterial loops (Fig. 6) or are interspersed between them (Fig. 2). Although the anterior episclera and conjunctiva drained towards the limbus (Fig. 4), this study revealed no well organised superficial venous ring corresponding to the anterior episcleral arterial circle.

The posterior conjunctiva drains back towards the tarsal circulation (Fig. 2).

The large episcleral vessels, which so often appear to pass no blood in conventional angiograms, were frequently seen to carry fluorescein during the late venous phase (Fig. 5).

TIMING

An angiographic sequence began with the appearance of fluorescein in the anterior ciliary arteries (Fig. 5). The filling of iris arterioles either coincided or followed within 2 seconds.

Filling of the anterior episcleral arterial circle took between 1·5 and 14 seconds. It is a variable anatomical entity and the interpretation of its limits inevitably influenced the delay that was recorded.

Anterior conjunctival arterioles fluoresced within

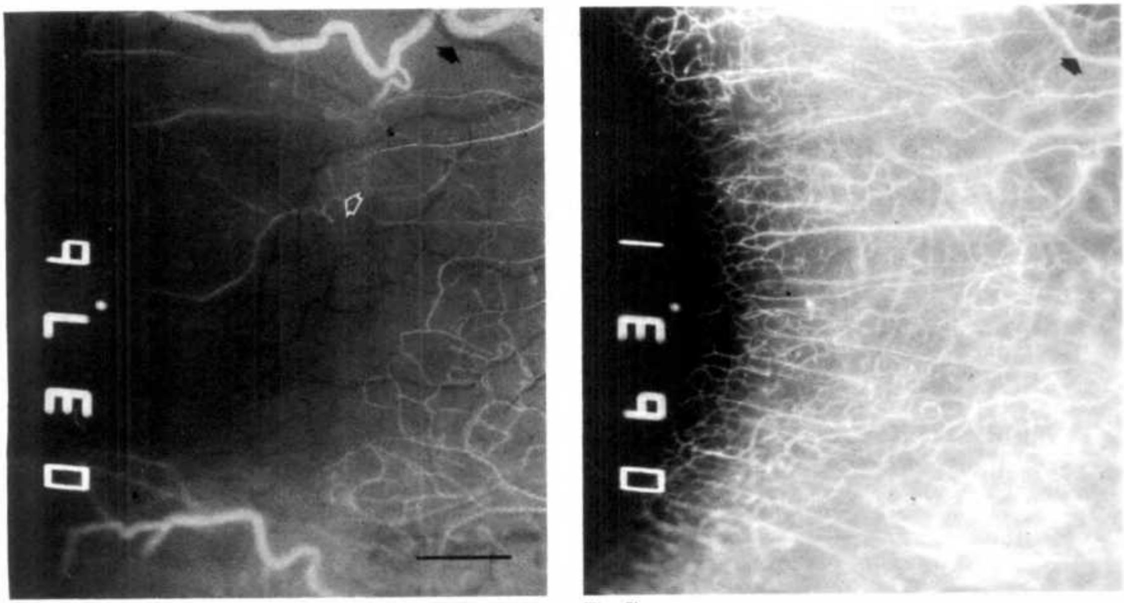

Fig. 5a

Fig. 5b

Fig. 5 *Right nasal angiogram of a normal 26-year-old male. (Scale=1 mm).* a *(6 seconds after first flush): Conjunctival filling from the posterior tarsal circulation precedes perfusion from the limbus. The large vessels that fill early are anterior ciliary artery trunks. Their divisions may penetrate the sclera, continue in the superficial episclera, or follow an intermediate course. One such vessel re-emerges from the sclera at (◊), where it contributes to the episcleral plexus and gives rise to a conjunctival arteriole. Note the large, non-perfused episcleral vessel (♦).* b *(31·5 seconds after first flush): There is complete filling of the limbal arcades, which do not leak. The deep vascular silhouette (♦) now fluoresces during the late venous phase.*

1·5 seconds after the segment of the anterior episcleral arterial circle that supplied them. Over the temporal globe this preceded posterior tarsal fluorescence by up to 4 seconds.

The times taken to fill the capillary plexuses are deceptive, since the episcleral plexus cannot be seen in its entirety, and the focusing of the angiogram may affect the definition of the limbal arcades. The most useful generalisations were that: all the capillaries seen in the angiogram were perfused between 6 and 30 seconds after first flush; the limbal arcades and the episcleral net filled most slowly.

Fluorescein sometimes appeared in conjunctival venules within 4 seconds of first flush and long before full perfusion of the capillary bed (see above). This made the distinction of venules from arterioles extremely difficult in some angiograms. Veins fluoresced correspondingly early (between 4 and 10 seconds after first flush), the first to do so being those draining the anterior conjunctiva.

The large episcleral veins usually filled late in the angiogram.

LEAKAGE

Leakage was first seen at between 4 and 10 seconds and its quantity varied widely. It was confined to capillaries of the conjunctiva and episclera (Fig. 6), and the walls of arteries and veins never stained. The limbal arcades did not leak for at least 30 seconds (Fig. 6), but free fluorescein entered the limbal zone at between 60 to 120 seconds, probably from the surrounding conjunctiva. The cornea never fluoresced.

There was minimal masking of anatomical detail before 30 seconds after first flush. When low dose anterior segment angiograms were repeated after an interval of 24 hours, insignificant background fluorescence persisted.

Discussion

By the simplest of modifications the technique of anterior segment fluorescein angiography has been considerably refined. Without interfering with the observation of arteries, the reduction in fluorescein dosage permits a reliable demonstration of the full sequence of capillary filling. Furthermore, the close association of fluorescein with albumin means that its immediate leakage always implies vascular pathology. The pattern of episcleral and conjunctival

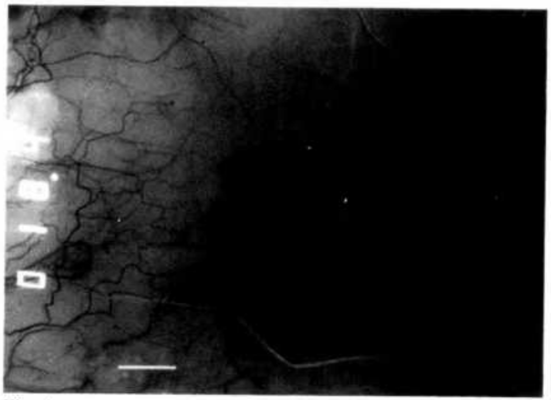

Fig. 6a

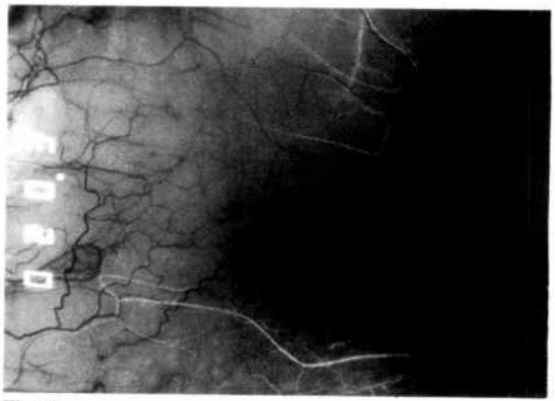

Fig. 6b

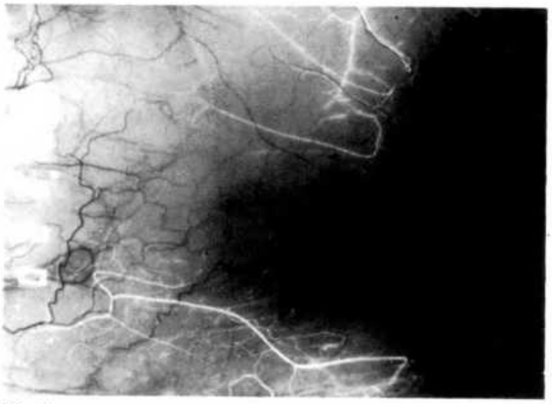

Fig. 6c

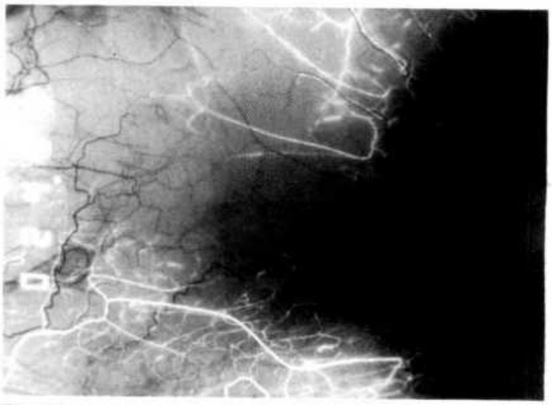

Fig. 6d

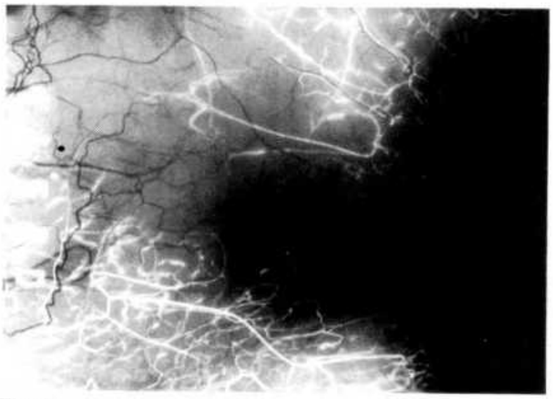

Fig. 6e

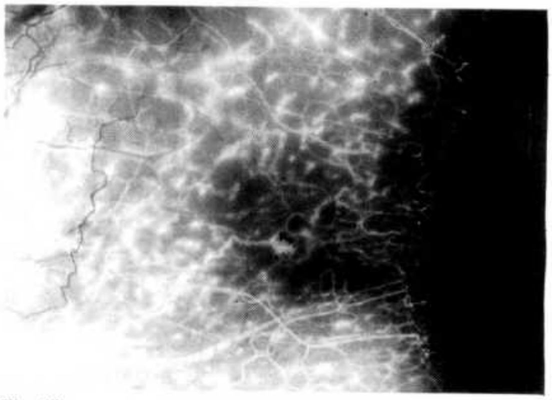

Fig. 6f

Fig. 6 *Right temporal angiogram of a normal 35-year-old male. Angiographic sequence from first flush: times recorded on film. (Scale=1 mm). Note the anastomosis between anterior ciliary and posterior tarsal circulations. An area of episclera far from any anterior ciliary artery trunk is perfused late in the angiogram from the adjacent episcleral plexus. The limbal arcades fill completely, 20 seconds after first flush and they do not leak fluorescein. Anterior conjunctival venules accompany the arterioles. Leakage of fluorescein from anterior conjunctival and episcleral capillaries begins at 4 seconds and is particularly brisk in this angiogram. However, there is still minimal masking of anatomical detail during the first 30 seconds.*

perfusion has been clarified and the venous circulation, hitherto obscured by early leakage, has now been revealed.

The technique that is outlined above was arrived at after experiments in which rabbits received low doses of fluorescein conjugates of dextran (molecular weight 70 000) intravenously. Leakage was avoided and high quality angiograms were obtained after the injection of as little as 5 µg fluorescein isothiocyanate per kg body weight (Meyer P, in preparation).

It is not only the photographic techniques that make such a reduction in dosage possible. Injected fluorescein isothiocyanate (FITC)-dextran conjugates remain within the intravascular compartment elsewhere in the body,[20] increasing the dosage to the eye. Furthermore the absence of leakage from anterior segment vessels heightens the contrast of the image. When FITC conjugates are approved for clinical use, FITC-dextran or FITC-human serum albumin will become the fluorescent probes of choice for anterior segment angiography. Until then, by restriction of the dose of sodium fluorescein to permit early and near-total ionic binding to serum albumin, we can approach this ideal state of affairs.

Although the partitioning of fluorescein between its free and bound forms strongly favours its association with albumin, approximately 10% of fluorophore remains free,[11] and that did inevitably leak from conjunctival capillaries. This was undetectable before 4 seconds, and never interfered with the interpretation of microvascular anatomy. Nevertheless, the dual problems of leakage and anatomical variation still preclude reliable estimation of relative flow rates in the anterior segment.

Because of its considerable variability, the circulation of the conjunctiva and episclera gives a random appearance, which anatomists have long attempted to clarify.[12 15 16] Despite differences between mammalian species, Morrison and Van Buskirk's elegant methacrylate casts of anterior segment vessels in the monkey are a useful starting point.[21]

The monkey anterior segment is perfused from an anterior episcleral arterial circle, fed by the anterior ciliary arteries. We consider its human counterpart, although asymmetrical and incomplete, to be equally crucial. Our angiograms show that it too arises from the anterior ciliary arteries, supplies the anterior conjunctival, anterior episcleral, and limbal circulations, and may also feed the iris arterioles. This concords with the anatomical descriptions of Leber[12] and Ashton and Smith.[15]

The episcleral arterial circle broadly resolves into superficial and deep components. This raises the possibility that its deeper component is the 'incomplete arterial circle' that Ashton and Smith described in association with the canal of Schlemm.[15]

The relationship between the episcleral arterial circle and the major circle of the iris cannot be resolved angiographically at present. Their simultaneous perfusion leaves no reason to doubt that they share a blood supply, but the relative contributions from the anterior and long posterior ciliary arteries must remain a matter of conjecture.

The anterior episcleral capillary bed is filled centrifugally by fine branches from the superficial or deep components of the episcleral arterial circle. However, these vessels feed only a narrow rim of episclera around the limbus. Beyond this the episcleral net is supplied by vessels that appear at the level of the rectus muscle insertions—probably branches of the anterior ciliary arteries. Perfusion of the zone separating these territories is tenuous, and the very frequent occurrence of scleritis in this region emphasises the importance of ischaemia to its aetiology.

The posterior limits of the territories of anterior conjunctiva and of episclera supplied by the episcleral arterial circle are superimposed. Closure of this common blood supply may explain why conjunctival infarction often overlies areas of severe scleritis.

The limbal arcades were completely perfused in all our studies, in contrast to the observations of Mitsui *et al.*[7] Vessels that filled late during their study were probably lost in the sea of background fluorescence. Until fluorescein had permeated the subconjunctival space, we found none in the limbal perivascular compartment. It may enter this region not by leakage from the arcades, but by diffusion from adjacent conjunctival capillaries.

The paradoxical paucity of anterior conjunctival venules in angiograms, despite their apparent profusion during slit-lamp examinations,[8] is simply explained once these vessels can be examined with adequate resolution. It transpires that the conjunctival capillary bed is arrayed in parallel between the radial arterioles and venules. Proximal capillaries fill first and shunt blood into conjunctival venules. Consequently, venous drainage close to the limbus precedes the arterial phase in the more distal conjunctiva: many of the radial conjunctival vessels that fill early are in fact venules. Blood flow through the distal anterior conjunctival circulation may be controlled by variations in the resistance within proximal capillaries.

Large vessels in which no flow can be recorded, previously considered to be a feature of the normal circulation,[9] were observed in the earlier frames of our angiograms. Bron and Easty[8] thought that they carried diluted fluorescein and became lost amidst the high level of background fluorescence that has hitherto plagued anterior segment angiography.

We can confirm this, since most of these vascular silhouettes did ultimately fill in our angiograms, and proved to be large veins.

The direction of flow within the anterior ciliary arteries is disputed. Some authors[9,19] have equated them with the 'emissary veins' described by Kiss in 1943,[17] in which blood appears to flow away from the limbus.[18] However, published angiographic sequences in which fluorescence of anterior ciliary arteries progresses centrifugally[10,19] can also be explained by poor illumination of the peripheral photographic field. Since the rate of flow in arterioles of 100 µm diameter is approximately 20 mm/s,[22] the resolution of this controversy is beyond the scope of this study, in which the minimum time interval between photographs was 1·5 seconds.

Although the filling sequence of the angiogram is reliably reproducible at any one site in a single individual, the timing varies enormously. There is also vast variation between subjects. This means that, even if a previous angiogram of the same area is available, the time taken for capillary beds to fill cannot be usefully compared.

Delayed perfusion has for some time been considered to be a hallmark of necrotising scleritis.[10] While this is true, the critical watershed zones can take 30 seconds to fill in normal people. Since capillary detail is lost by that time in many full-dose angiograms, they must be interpreted with great caution.

The low dose of fluorescein that we administer should reduce the morbidity of fluorescein angiography. Indeed no adverse effects have yet been recorded during any of the 30 angiograms that we have so far performed.

Capillary beds that usually leak fluorescein may now be examined by fluorescein angiography. This paper offers an introduction to the angiographic appearances of the anterior segment of the normal eye, but the method is equally applicable to the observation of circulations exposed at surgery or endoscopy.

We thank Mr K Harvey for his help with the development of the photographic techniques and Miss C Barber for photographing the angiograms.

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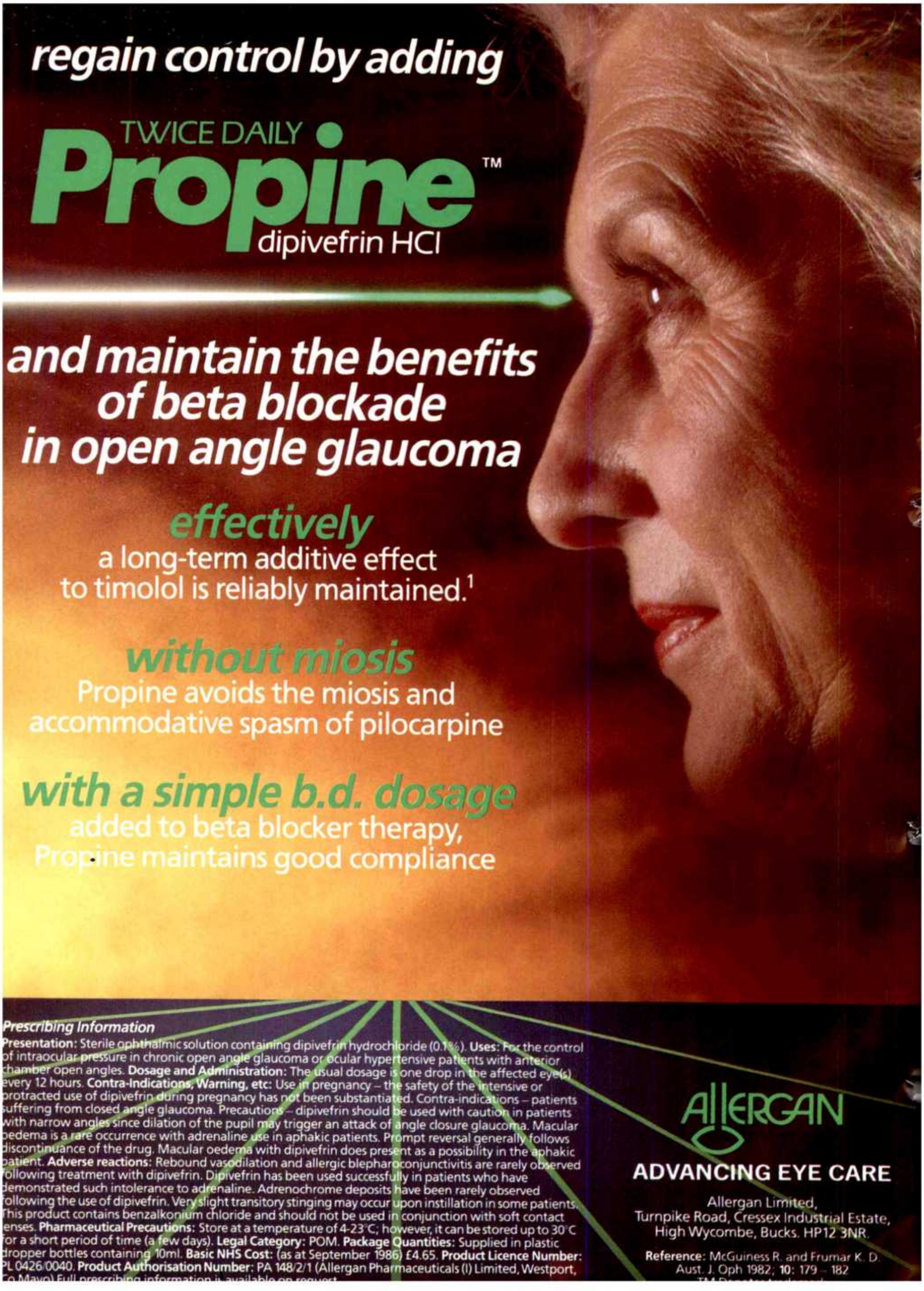

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Treatment of Mooren's ulcer with cyclosporin A: report of three cases

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SUMMARY Three patients with severe, bilateral, progressive Mooren's ulcers, unresponsive to medical and surgical therapy, were treated with cyclosporin A. All three responded rapidly to the drug and there has been no recurrence of the Mooren's ulcers since (average follow-up 14 months). Peripheral blood T lymphocyte subsets were estimated prior to and during treatment. No significant abnormalities were found initially. Suppressor cells increased on treatment, and a corresponding drop of the helper/suppressor cell ratio occurred in two patients.

Mooren's ulcer is a chronic painful ulceration of the corneal periphery. There is a steep, undermined leading edge to the ulcer, which spreads both circumferentially and centrally, eventually involving the whole cornea. Clinically, two different types of Mooren's ulcer have been recognised.[1 2] A limited type occurs unilaterally in older patients; progression can be halted by various surgical treatments, including conjunctival excision and lamellar keratoplasty. The other type of Mooren's ulcer is relentlessly progressive, often bilateral, and occurs in younger patients, particularly males. There is involvement of the sclera as well as peripheral cornea, perforation occurs more commonly, and both surgical and medical treatments are unsatisfactory, with the ultimate prognosis being poor.[1]

The aetiology of Mooren's ulcer is unknown, but recent evidence suggests an autoimmune process is responsible. Circulating antibodies to human corneal and conjunctival epithelium have been found in a patient with Mooren's ulcer.[3 4] Histologically the conjunctiva is found to be heavily infiltrated with plasma cells and lymphocytes.[2] Direct immunofluorescent techniques have demonstrated immunoglobulin localised to the conjunctival epithelium, complement also being found in active cases.[4] The presence of collagenolytic and probably proteoglycanolytic enzymes in the conjunctiva adjacent to the Mooren's ulcer indicates that this tissue is intimately associated with the pathogenesis.[5] The source of these enzymes is probably from mononuclear cells and neutrophils found in and around the ulcerating tissues.[5 6]

Evidence that cellular as well as humoral autoimmune phenomena are found in Mooren's ulcer has been demonstrated by positive macrophage migration inhibition in response to corneal antigen presentation to lymphocytes from patients with the disease.[7] Murray and Rahi[8] found a deficiency of suppressor T lymphocytes in the peripheral blood of a patient with Mooren's ulcer. They postulated that this deficit in the immunoregulatory mechanism explains some of the immunological abnormalities reported in previous studies and also provides additional evidence for an autoimmune aetiology. Furthermore an increase in circulating immune complexes in patients with Mooren's ulcer has been reported.[9]

The presumed autoimmune aetiology and the poor response to conventional treatment, especially of the progressive type of Mooren's ulcer, has led to the use of immunosuppressives in an attempt to control the disease. Foster *et al.*[6] used methotrexate for six weeks in one patient with a good response, and no recurrence occurred during the subsequent 12 months. The authors suggested immunosuppressives should be given early in the disease. In a second patient Foster[10] reported only partial success with this agent and cyclophosphamide was then used. However, recurrence occurred when the dose of this drug was reduced after six months.

Murray and Rahi[8] suggested that treatment should

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be directed towards correction of the T lymphocyte helper/suppressor ratio by giving one of the thymic hormones or alternatively cyclosporin A (CSA). This paper presents three patients with the progressive type of Mooren's ulcer who were treated with CSA successfully.

Patients and methods

Three patients with severe bilateral Mooren's ulcers of the progressive type, were treated with CSA (Table 1). All were unresponsive to conventional therapy. Initially topical antibiotics and acetyl cysteine 10% were given. When these failed to halt the disease topical corticosteroids were administered, and finally conjunctival peritomy and cryotherapy were performed to the conjuctiva adjacent to the ulcer. These surgical measures provided some temporary relief, but within a week the ulcers progressed again. Before administration of CSA two eyes perforated. An onlay lamellar graft was performed on one; the other perforation was sealed with cyanoacrylate glue. After failure of the above regimen oral CSA was started.

The patients were all healthy black males with no systemic disease. No biochemical abnormalities were detected on screening; in particular serum creatinine, urea, and liver function tests were normal. Urine analysis and creatinine clearances were also normal. Initially CSA was given as a loading dose of 8 mg/kg/day in two divided doses for two days. Thereafter, the dose was reduced to 3–4 mg/kg/day, the dose being adjusted to maintain trough serum levels of 200–400 ng/ml. Biweekly tests of trough serum CSA levels, serum creatinine, urea, and liver function were performed. Creatinine clearance was tested weekly.

During CSA treatment all other medication was stopped except topical antibiotics. Before and during the course of treatment the following immunological parameters were investigated. T lymphocyte subsets were measured on a fluorescence activated cell sorter, immunoglobulins and complement C3 and C4 were measured by nephelometry, and immune complexes were estimated by the Clq binding assay. All the patients lived in rural areas and were admitted to hospital for treatment. CSA was tailed off and stopped after six weeks, and two of the patients were discharged. Case 3, who was monocular, elected to remain in hospital to have a corneal graft (see below).

Table 1 *Clinical details of patients*

	Age (years)	*Duration of disease prior to CSA (weeks)*	*Period of CSA therapy*	*Follow-up (months)*	*Remarks*
Case 1	62	7	6 Weeks	16	Free from Mooren's ulcer
Case 2	65	5	6 Weeks	12	Free from Mooren's ulcer
Case 3	58	8	5·5 Months	14	Free from Mooren's ulcer, Graft clear

Results

CASE 1

A 62-year-old man presented with a three-week history of excruciating pain. He had bilateral Mooren's ulcers involving 160° and 130° of the right and left corneal peripheries respectively. Centrally the corneas were clear, with visual acuities of 6/9 right and 6/6 left. The ulceration continued to progress on medical therapy and was only temporarily halted by conjunctival peritomy and cryotherapy. The pain continued unabated. CSA was started. Within three days the pain had completely subsided, and by the end of the first week the ulcers ceased progressing. At one month the eyes were quiet, the ulcers had partially filled in, and an intact epithelial layer was present. Treatment was tailed off and stopped after six weeks. The Mooren's ulcers have not recurred in the 16-month follow-up. His visual acuities are 6/6 right and left corrected.

CASE 2

A 65-year-old man presented with severe pain and loss of vision in both eyes of one month's duration. His visual acuity was hand movements in both eyes. Bilateral 360° ring Mooren's ulcers were present with central islands of scarred cornea (Fig. 1). The left eye had perforated inferiorly; cyanoacrylate glue was applied to seal the leak. Medical treatment was instituted, but because of the danger of further perforation bilateral 360° conjunctival peritomy and cryotherapy was performed. This gave temporary relief, but within a week the ulceration was again progressing. CSA was started, and within four days the pain had subsided and by a week the ulcers had stopped progressing. At a month his eyes were quiet and the ulcers had partially filled in, with an intact epithelial layer. After six weeks the CSA was tailed off and stopped. Eleven months later he remained free of disease, but his corneas were opaque and vascularised (Fig. 2). A right combined keratoplasty and lens extraction was performed.

CASE 3

A 58-year-old man was seen with a phthisical right eye. He gave a history highly suggestive of an old perforated Mooren's ulcer. His left eye had become painful a month previously, and his vision had

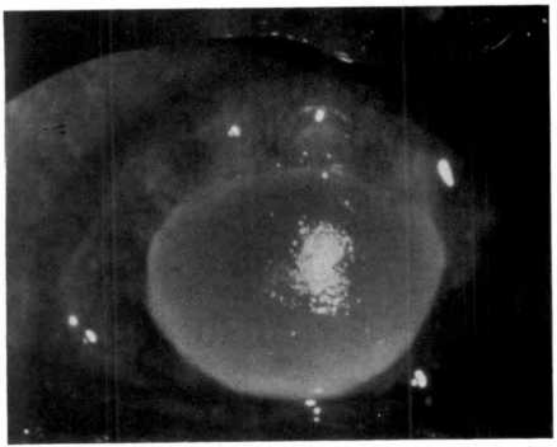

Fig. 1 *Case 2, Mooren's ulcer involving the entire corneal periphery of the right eye. The central cornea is opaque.*

deteriorated to hand movements. There was a 270° Mooren's ulcer with a perforation. The central cornea was opaque. A patch lamellar graft was applied and topical medication started. During the next two weeks the ulcer progressed to a ring ulcer, and the graft was absorped. Conjunctival peritomy and cryotherapy provided some respite, but within a week the disease was again progressing. CSA was started, and by the third day the pain had gone and by a week the ulcer was healing. After one month the eye was quiet, with the ulcer partially filled in with an intact epithelial layer. The central cornea remained opaque, and at six weeks he elected to remain in hospital for a central corneal graft. CSA was continued, and prednisone 25 mg daily was started to prevent rejection of the graft in this highly vascularised corneal bed. CSA and prednisone were tailed off and stopped four months postoperatively. When seen 14 months later his graft remained clear, his visual acuity was 6/12 corrected, and there had been no recurrence of his Mooren's ulcer.

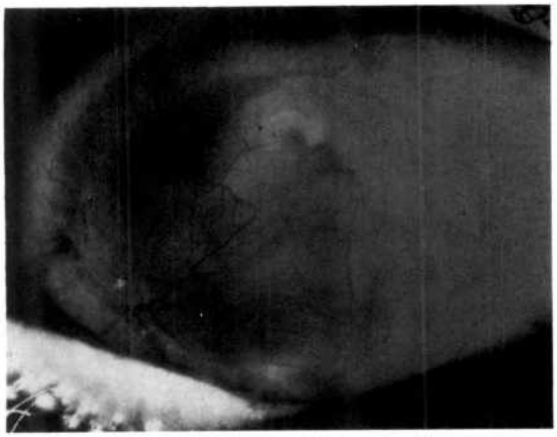

Fig. 2 *Same eye as in Fig. 1 11 months later. The eye is quiet, the ulcers have filled in, but the cornea is opaque and vascularised.*

Within four days of starting CSA treatment all three patients were free from pain. By the end of the first week the ulcers had stopped progressing and showed evidence of healing. After four weeks all the eyes were quiet, the stroma comprising the base of the ulcer was thicker, and, although furrows remained, an intact epithelial layer was present. All the eyes have remained quiet and free from a recurrence of Mooren's ulcer and the corneal graft in case 3 remains clear. The average follow-up is 14 months (range 12–16 months).

HISTOLOGY AND BIOCHEMISTRY

Histological examination of the excised conjunctiva from all three patients revealed findings consistent with a diagnosis of Mooren's ulcer.[5 6] In all specimens neutrophils, lymphocytes, and large numbers of plasma cells were present in the subepithelial layers.

The serum IgA was raised (Table 2) in all three patients. This is in keeping with other studies that have reported raised levels of IgA in Mooren's ulcer.[11 12] In case 2 the level 11 months after treatment was reduced but still above the normal range, despite his being clinically free of the disease. Case 3 showed decreasing values of IgA while on cyclosporin. IgM levels were normal in all our patients. Cases 1 and 3 had normal IgG values, but in case 2 it was raised. No significant abnormalities were found in the level of complement values C3 and C4. Circulating immune complexes were normal in all three patients.

Estimations of total T lymphocytes (OKT 3, Ortho Diagnostics) were within the normal range in all patients (Table 2). Helper T cells (OKT 4) were also within normal limits. Suppressor T cells (OKT 8) were in the normal range initially and rose during CSA treatment. The rise was most marked in case 3. The helper/suppressor ratio was initially normal in all three patients and dropped in cases 1 and 3; the change was more marked in the latter. In case 2 the ratio remained essentially constant during treatment and 11 months later.

No significant side effects of treatment were encountered. Serum creatinine and urea rose in all three patients but did not exceed the upper limits of normal. Dosage of CSA was adjusted to keep serum levels within the therapeutic range, without allowing creatinine to rise excessively. No abnormalities in liver enzymes or blood cell counts were detected. Creatinine clearances dropped but again remained within normal limits in all three patients. Other

Table 2 *Immunological parameters*

Immunological Parameter	*IgA*	*IgM*	*IgG*	*C3*	*C4*	*Immune complexes*	*OKT3*	*OKT4*	*OKT8*	*4/8 Ratio*
Normal values	72–312	56–352	639–1349	83–177	15–45	0–7 (% binding)	59–91 (%)	32–65 (%)	16-38 (%)	1·2–3·0
Case 1										
Pre-CSA	346	146	871	191	54·2	3·7	60·6	42·1	26·4	1·59
CSA	—	—	—	138	16·4	—	68·8	39	33·7	1·16
Case 2										
Pre-CSA	490	294	1910	105	40·3	3·8	64	38	25	1·55
CSA	—	—	—	—	—	—	72	46	29	1·75
Post-CSA (11 months)	460	230	2520	—	—	—	72	48	26	1·79
Post-CSA (12 months)	—	—	—	—	71	42	29·5	1·64		
Case 3										
Pre-CSA	318	269	1250	—	—	4·0	—	—	—	—
CSA (one week)	—	—	—	—	—	—	67	43·3	24·3	1·78
CSA (one month)	—	—	—	—	—	—	77	42	22·7	1·85
CSA + steroids (one month)	263	228	955	85	19·8	—	77·3	46·7	24·8	1·88
CSA + steroids (two months)	259	230	955	99·4	42·8	—	81	44	37·8	1·18
CSA + steroids (three months)	272	222	1090	78·9	25·4	—	76·6	32·4	43·4	0·74

known side effects of CSA therapy such as neuraesthesia, gum hypertrophy, tremor, or lymphoma did not occur.

Discussion

Our patients, all black males, had clinical and histological evidence of Mooren's ulcer. Standard medical and surgical treatments had failed to halt the disease. In all the cases the disorder was bilateral, one patient having lost an eye. In another two eyes perforation occurred—a total of three perforations in the six eyes (50%). The disease was undoubtedly of the serious, progressive type that is resistant to treatment, though our patients were older than people in whom the progressive type usually occurs.[12,13] None of the patients had evidence of anklyostomiasis, a disease implicated in the high incidence of the progressive type of Mooren's in other parts of Africa.[2,13]

All our patients had raised IgA levels. Mondino *et al.*[11] and Mondino[12] found 56% and 63% respectively of their patients with Mooren's ulcer had raised levels of this immunoglobulin. Immune complexes were found to be normal by the CIq binding assay. This is in keeping with the finding by Berkowitz *et al.*[10] of normal levels in patients in Mooren's ulcer using this assay, though higher levels were found using the Raji cell assay.

The totals of T lymphocytes were in the normal range. Similarly the helper cells showed normal values. Towards the end of the longer period of CSA therapy given to case 3 the level dropped significantly. The most consistent response to treatment was observed in the level of suppressor cells, which rose in all patients. This is the expected response to CSA treatment. A drop in the helper/suppressor ratio was found in cases 1 and 3. In case 2 the helper cells increased, as did the ratio. None of our patients had low levels of suppressor cells initially, in contrast to the findings of Murray and Rahi[8] in their patient. The most marked changes in the lymphocyte subsets were found in case 3, who had a longer course of CSA therapy. These changes occurred when corticosteroids were introduced after his keratoplasty, and may be partly explained by a potentiating effect of steroids on CSA.

The most dramatic effects of CSA treatment were clinical. Within four days all three patients were free from pain and remained so. This was in contrast to the medical and surgical treatments that did not relieve the pain that had been present from five to eight weeks prior to CSA therapy.

The effect on the ulcer was no less dramatic. Within a week the ulcers stopped progressing and the eyes were quieter. After four weeks the eyes were not inflamed and the ulcers had partly filled in, leaving shallow furrows with intact epithelial coverings. No recurrence has followed the stopping of CSA (average follow-up 14 months).

The poor response to other treatments and the rapid response to CSA suggests that this drug is an effective treatment for Mooren's ulcer. Provided improvement occurs as rapidly as in our patients, a six-week course appears to be sufficient to halt the disease and prevent recurrence, as shown by cases 1 and 2. Its mode of action is not entirely clear.

We were unable to demonstrate a deficiency of suppressor cells in our patients.

CSA inhibits the activation of the helper (OKT4) subset but does not inhibit the activation of suppressor cells (OKT8). This differential effect on different T cell subsets results in a fall in the OKT4:8 ratio during treatment. Because 'help' is required for the activation of the cytotoxic subset the drug secondarily inhibits cytotoxic cell formation.[14] CSA also inhibits the pathway of primary T cell activation by interfering with the transmission of the antigen specific signal to the interior of the cell, following antigen binding.[15] The efficacy of CSA in animal models of autoimmune diseases has been summarised by Borel.[16] While some animal models of autoimmunity were improved by CSA therapy, others deteriorated. Published studies of the efficacy of CSA in human autoimmune diseases are limited, but promising results have been obtained in some cases, including the use of CSA in Graves's ophthalmopathy[17] and uveitis.[18 19] There are no other published studies on the efficacy of CSA in the treatment of Mooren's ulcer.

CSA is a potent drug with potentially severe side effects including nephrotoxicity, hepatotoxicity, and occurrence of lymphoma. A recent report[20] indicates that nephrotoxicity may be avoided by monitoring serum creatinine and trough CSA blood levels, with corresponding adjustments of the administered dose. By taking these precautions, and also performing serial tests of liver function and creatinine clearance, side effects can be kept to a minimum. The risk of neoplasia with CSA appears to be no greater than with other immunosuppressive regimens.[21] Apart from small increases in serum urea and creatinine, which remained within normal limits, no side effects were encountered in this study.

Mooren's ulcer is a sight threatening disease, especially when progressive and bilateral. The associated pain is also severe. Under these conditions immunosuppression is justified if the drug is carefully monitored and side effects can be prevented or minimised. In our three patients CSA appeared to be effective, but this is a very small study. To prove its efficacy a larger, controlled trial will be necessary. However because Mooren's ulcer is a rare disorder a trial of this type may be difficult to organise.

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Acquired posterior keratoconus

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SUMMARY A case of acquired posterior keratoconus is presented. As in developmental cases the vision was moderately reduced and the condition was not progressive. Posterior keratoconus is usually developmental in origin, but trauma has been implicated in some cases.

Posterior keratoconus is a rare corneal disorder characterised by non-inflammatory thinning of the cornea, resulting in a conical protuberance of the posterior surface. The anterior surface remains regular, so differentiating the condition from anterior keratoconus. It is usually considered to be a developmental abnormality.

Case report

A white male was known previously to have had 6/6 vision in both eyes, unaided, and with normal globes. The eyes had been assessed for occupational purposes. At the age of 25 years he suffered a right penetrating injury from the impact of a metal spring. The resulting small corneal perforation did not require surgical treatment, but a secondary cataract developed. This was treated by needling via a limbal approach. At the age of 27 years he was assessed for contact lens correction of his right aphakia. His right visual acuity was then 6/18 with refraction +11·00 D sph, −1·00 D cyl axis 85° BVD 11 mm, and keratometry 7·45 axis 5°, 7·80 axis 90°. Posterior corneal thinning was noted. He initially wore a contact lens, but after 18 months he abandoned this and was lost to follow-up treatment.

He returned at the age of 38 years, when he was asymptomatic but again required a contact lens to correct the right aphakia. The right cornea remained regular anteriorly, but the posterior conical protuberance and hazy posterior stromal opacity were still present (Fig. 1). The posterior cone was 3 mm in diameter and its apex was 2 mm, nasal and inferior to the centre of the cornea. The appearance was consistent with the drawing made at initial presentation. No abnormality of the iris or angle was detected. The right visual acuity was 6/18 with refraction +10·00 D sph −1·50 D cyl axis 30° BVD 11 mm, and keratometry 8·10 mm axis 30°, 7·60 mm axis 120°. The ocular media were clear and the optic disc and macula also appeared normal. The left eye had a visual acuity of 6/6 unaided; keratometry was 8·20 mm axis 30°, 8·15 mm axis 120°, and the anterior segment was normal. Photokeratometry showed the anterior corneal surface to be regular. The central corneal thickness was 0·52 mm in both eyes; in the right this was at the temporal edge of the cone, and the corneal thickness at the cone apex was 0·23 mm.

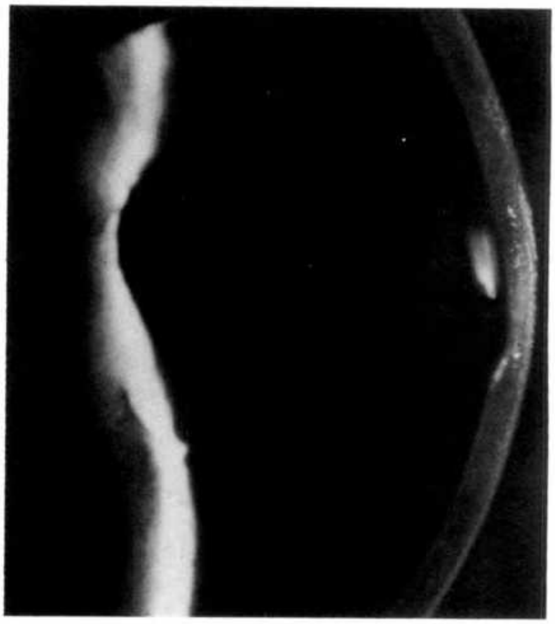

Fig. 1 *Slit-lamp photograph of acquired posterior keratoconus.*

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Discussion

Posterior keratoconus was described by Butler in 1927.[1] The posterior corneal protuberance is mostly localised, central, and associated with posterior stromal opacity.[2 3] The visual loss is not progressive[3] and is only moderate.[4] If marked visual loss occurs, another cause must be sought, as has been illustrated by a case of Schocket *et al.*[5] A Fleischer ring may be present.[6]

Posterior keratoconus is usually considered to be a developmental defect because half the cases are bilateral, and it has been reported in two siblings and also in a parent and child.[2 3] Krachmer and Rodrigues[6] consider it to belong to the spectrum of anterior cleavage syndromes, as it is frequently associated with other anterior segment anomalies.[7]

Trauma has been proposed as an alternative cause,[8] but before the present case there has been little to support this theory. A history of trauma or ocular disease was present in a minority of cases in one review.[3] However, there were no details of the trauma or the prior visual acuity or corneal appearance, so the history of trauma may be coincidental.

This case shows that some cases of posterior keratoconus may be acquired as a result of trauma. The mechanism in such cases may involve an oblique penetrating injury, with more splitting and destruction of the inner corneal layers than the outer. Alternatively localised damage to Descemet's membrane or the corneal endothelium may be involved. Either mechanism is likely to be modified by later corneal remodeling. In this case keratometry showed an increase in radius of corneal curvature and the refraction altered, but there was no progression of the visual loss.

I thank Mr R J Buckley for his advice and for permission to report a patient in his care.

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Cyclic variation in onset of central retinal vein occlusion

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SUMMARY We studied the seasonal incidence of onset of symptoms of central retinal vein occlusion (CRVO) in 105 patients over a 5-year period. Their onset showed a significant cyclic variation ($p<0\cdot01$), being most frequent in the months September through to February. We believe this seasonal variation may in part reflect seasonal changes in haemostasis and retinal perfusion, though other unidentified factors play a significant rôle.

Although central retinal vein occlusion (CRVO) is a relatively common disorder, its aetiology remains unknown. It is often associated with endogenous disease such as atheroma, diabetes mellitus, and raised intraocular pressure,[1] and exogenous factors are not known to influence its onset. Theories of origin include endothelial swelling,[2,3] arterial hypoperfusion,[4] and thrombotic venous occlusion.[5] The debate on the primacy of arterial versus venous factors in the genesis of CRVO is not resolved.[4,6,7] Since systemic arterial diseases such as peripheral arterial emboli,[8] myocardial infarctions, and cerebrovascular accidents[9] show a seasonal variation related to temperature, while systemic venous diseases do not,[9] we studied the seasonal variation of CRVO in order to gain clues to its origin.

Patients and methods

Patients with a CRVO were identified from the fluorescein angiography index file at the Western Ophthalmic Hospital. Only consecutive new cases with dates of onset between September 1979 and the end of August 1984 were included. Patients' notes were traced and the date of onset of symptoms was recorded, as were each patient's age and sex. Patients were included only if a CRVO was shown on fluorescein angiography and an accurate date of the onset of symptoms was noted. Cases were classified as ischaemic or non-ischaemic on the basis of the fluorescein angiogram. The monthly incidence of CRVOs was charted and the results analysed.

The method of Edwards[10] was used to test for the presence of cyclic variation.

Results

The frequency of onset of CRVO was much greater in the six months from September to February (72 cases) than in the subsequent six months from March to August (33 cases, Fig. 1). The distribution was bimodal, with peaks occurring in September and February. The annual variation was similar for both ischaemic and non-ischaemic CRVOs. There was no clustering by age or sex. The variation was present in all years.

By Edwards's method the frequency of onset of CRVO shows significant cyclic variation ($p<0\cdot01$). When the six-month period with the greatest frequency of cases (September to February) was compared with the six months March to August, a significant difference was found ($\chi^2=14\cdot48$, $p<0\cdot001$). A weak inverse correlation with the monthly temperature was noted ($r=-0\cdot48$). A weak positive correlation with the monthly frequency of deaths from respiratory disease in England and Wales (1962 to 1964) was found ($r=0\cdot50$).[9] Correlations with

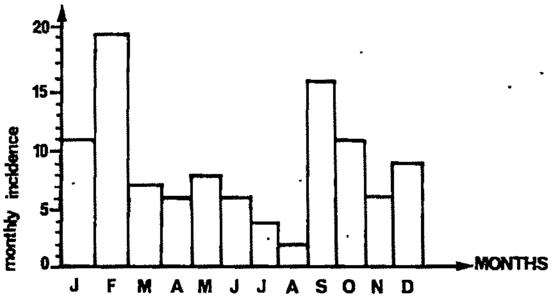

Fig. 1 *Monthly incidence of onset of central retinal vein occlusion over five years in 105 cases.*

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published figures of the seasonal variation in myocardial infarction[9] (r=−0·23), peripheral arterial emboli[8] (r=−0·23), and arterial blood pressure[11] (r=0·25) were poor.

Discussion

The epidemiology of CRVO is characterised by a nocturnal onset and a peak frequency in the 7th decade of life, with less than 10% of patients under the age of 40 years.[7] We also found a significant annual variation, suggesting that exogenous influences may be important. We are not aware of any previous reports of an annual variation in CRVO onset.

The bimodal peak suggests that different factors may account for the excesses seen in September and February. If the first peak is ignored, the variation in onset of CRVO is very similar to the variations in temperature for the period 1979 to 1984. This suggests that the February excess and summer paucity of cases of CRVO may be related to environmental temperature changes, though separate factors must explain the September peak.

A seasonal incidence of CRVO may be compatible with a thrombotic aetiology. Myocardial infarctions and cerebrovascular accidents are more frequent in winter than other seasons and show close correlations with temperature.[8 9] Cold temperature is associated with a decrease in blood levels of antithrombin 3, with increased risk of thrombosis,[12] and CRVO is a disease of the elderly, who have impaired thermoregulatory mechanisms.[13] In addition exposure to cold increases both whole blood and plasma viscosity, the volume of plasma occupied by platelets, and the arterial blood pressure.[14] It is likely that seasonal variations in blood pressure[11] and haemostatic factors,[12] perhaps induced by changes in core body temperature, are partly responsible for the variation in onset of CRVO found in this study. However, this would not explain the early peak seen in September.

Patients with CRVO are known to have a high incidence of associated systemic diseases, including chronic obstructive airways disease (COAD).[15] COAD displays well recognised winter exacerbations, which are associated with increasing hypoxia. Hypoxia impairs red cell deformability and increases red cell viscosity,[16] and this will alter blood flow properties. In addition hypoxia increases retinal vasodilatation, and in the presence of arterial insufficiency this may precipitate stasis, leading to vascular occlusion.

Endothelial swelling has been thought to play a part in the pathogenesis of CRVO,[2] and together with the seasonal incidence found in this study it might be interpreted as evidence for an infectious aetiology. While a number of virus infections show a winter peak, a bimodal peak in September and February could not be identified in virological records (Public Health Laboratory, Colindale, personal communication, 1985). Although C-reactive protein levels (a non-specific indicator of inflammatory activity) are increased in CRVO patients as compared with controls,[17] the elevation is very modest and not at the levels seen in inflammatory disease. Moreover, recent histopathological studies discount the role of inflammation in ischaemic CRVO, showing rather that thrombosis is the primary event, with an inflammatory cell infiltrate occurring secondarily in response to clot formation.[5]

Raised intraocular pressure contributes to the development of a CRVO.[1] We are not aware of any studies of seasonal variation of human intraocular pressure, though studies of the rabbit have shown small seasonal variations with peaks in summer and winter.[18] Such small variations are unlikely to be relevant to the question of human CRVO.

The question must arise whether these results are an artefact. All our patients had presented directly to the Western Ophthalmic Hospital, and secondary referrals were not included. Consultant policy regarding fluorescein angiography has not changed significantly during the period studied. Attendances at the Casualty Department show a very small seasonal variation (with a summer peak), which does not account for our findings, particularly as patients presented at widely varying intervals after onset of CRVO. Data were collected in a randomised and unbiased fashion. When the results were plotted for sequential years the seasonal variation was seen with each successive graph.

However, certain possible sources of error do exist. This was a retrospective study, and patients were seen by a variety of doctors, which may have resulted in errors of dating onset, and many patients with CRVO were not included because the date of onset was not known. These factors are unlikely to explain our findings, since they would be expected to provide a constant error. Further, CRVO may often be asymptomatic, with symptoms supervening only when macular oedema or increasing ischaemia occurs. The variation we have recorded could therefore be a reflection of factors influencing visual function in patients with CRVO rather than onset of CRVO.

It is possible that our findings apply only to a specific subset of CRVO. In our study 43% of patients had severe, ischaemic CRVOs as compared with a general incidence of 22% of all CRVOs.[7] The weighting in favour of the more severe forms of CRVO is not surprising, since this study required a definite date of onset of symptoms and fluorescein angiography, which are features far more frequent in severe CRVOs. Although we found no difference in the seasonal incidence of CRVOs classified as ischaemic or non-ischaemic, it is possible that in some patients we have measured the onset of symptoms in longstanding, previously asymptomatic CRVOs.

While the cyclic trends in CRVO are similar to those in arterial diseases in having a relative paucity of summer cases, with an excess in the colder months, the bimodal incidence of CRVO is clearly different and correlated poorly with the actual incidence of arterial emboli, suggesting the influence of several factors.

To elucidate further the aetiological factors in CRVO, longitudinal studies need to be performed to document the history accurately and to identify blood rheological and clotting abnormalities. Such studies may allow the further characterisation of an at-risk population. Insight into the pathophysiology of CRVO could permit the design of specific therapy.

In conclusion, we have demonstrated a significant cyclic variation in the onset of CRVO, suggesting that exogenous factors may be important in its pathogenesis in addition to the well recognised association with endogenous disease. It is likely that part of this variation reflects temperature associated changes in haemostasis and retinal perfusion, though the early peak is not explained.

We thank Mr Ron Marsh for encouragement and access to records, and Sir Stanley Peart for helpful comments. We are grateful to Ms Karen Johnstone for the figure.

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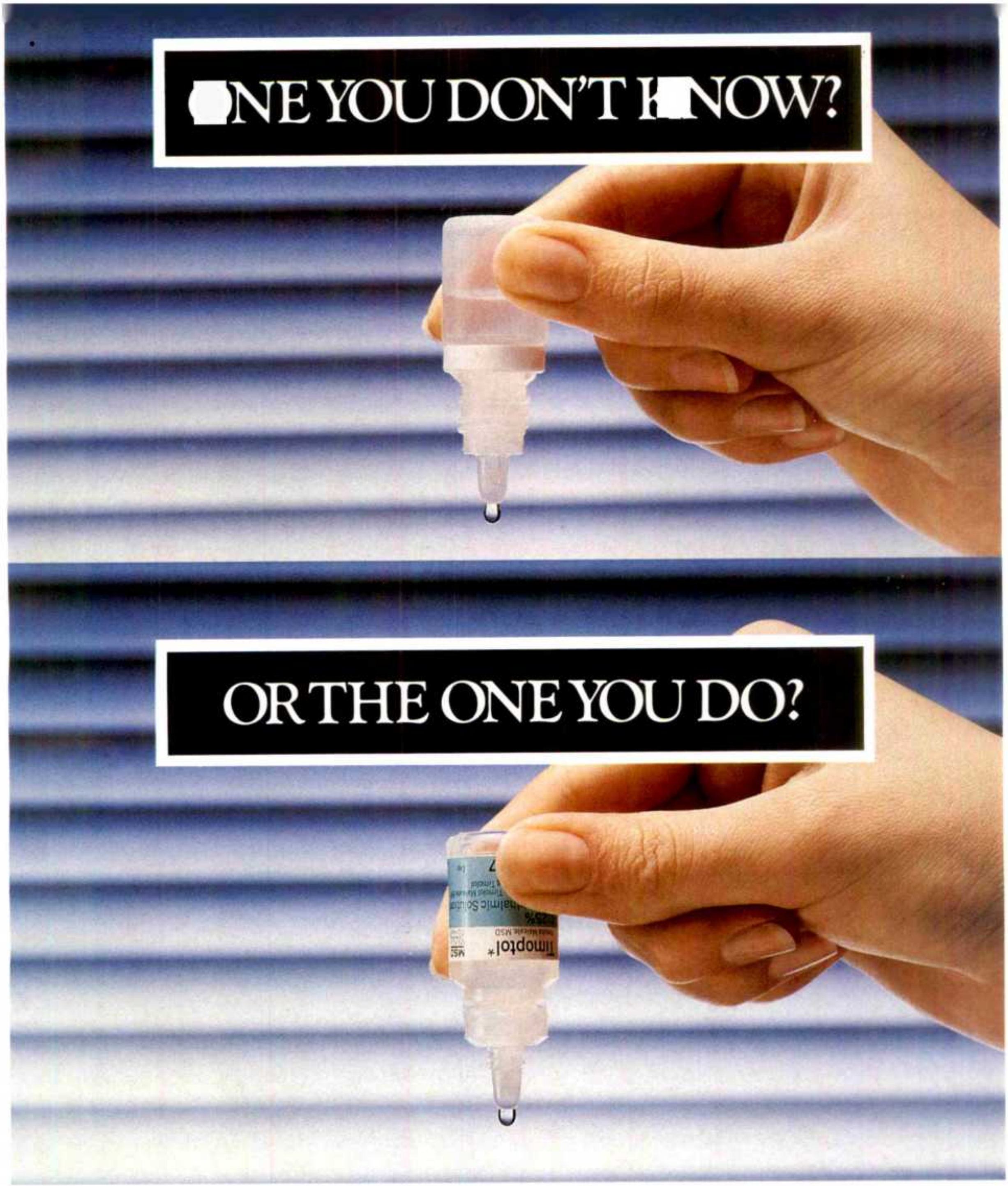

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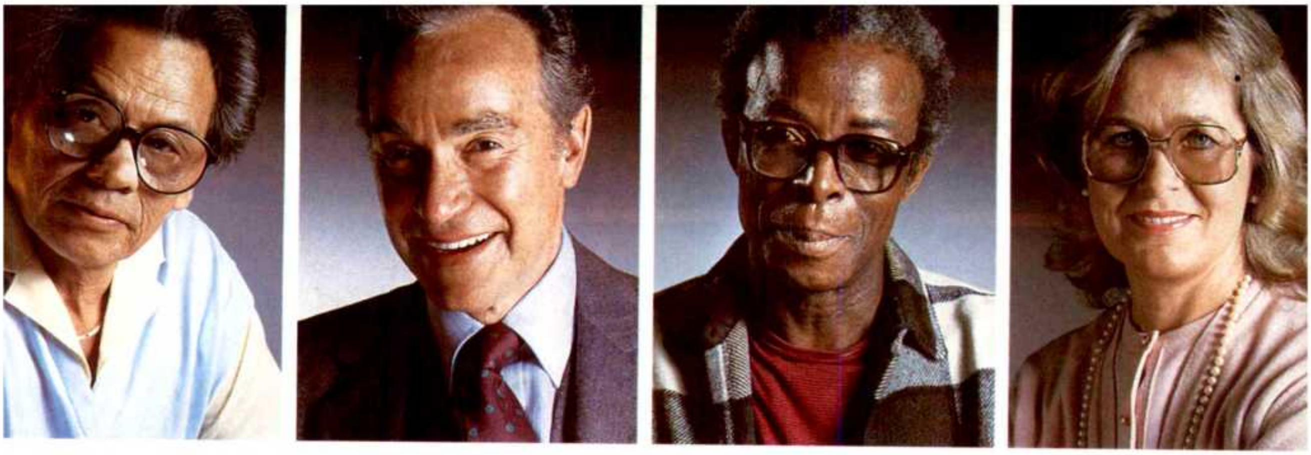

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Nerve fibre layer loss in diseases of the outer retinal layer

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SUMMARY We present examples of nerve fibre layer changes in diseases thought to affect primarily the outer retinal layers. These disease processes include cone-rod dystrophies, rod-cone dystrophies, juvenile macular degeneration (Stargardt's disease) and fundus flavimaculatis, vitelliform macular dystrophy, and Leber's congenital amaurosis. All were associated with alterations in the retinal nerve fibre layer, either diffuse or focal. The presence of these nerve fibre layer changes raises the question of transsynaptic degeneration and of possible primary or associated disease of other retinal cells than the receptors—namely, bipolar, amacrine, Mueller, or ganglion cells—in these diseases of the outer retinal layer. Involvement of the nerve fibre layer also indicates the need to examine patients with defects in the nerve fibre layer by electroretinograms and other tests for outer retinal layer disease when no obvious optic nerve disease is present.

Clinically manifest damage to the anterior visual afferent pathways, especially the optic nerve, usually causes visible changes in the retinal nerve fibre layer. Not infrequently loss of the retinal nerve fibre layer gives the first clue of optic nerve compromise in glaucoma or multiple sclerosis and precedes the clinical manifestations, visual symptoms, or the visual field deficits.[1-3] The changes in the retinal nerve fibre layer secondary to optic atrophy are quantitative changes, which appear as diffuse or focal atrophy of the nerve fibre layer.[4] Qualitative changes in the nerve fibres themselves may be seen prior to optic atrophy and are characteristic of some diseases, such as Leber's hereditary optic atrophy.[5]

A number of ocular disorders known to involve primarily or exclusively the outer retinal layers are also associated with atrophic changes in the nerve fibre layer. To illustrate this point we present below examples of retinal receptor and/or pigment epithelium disorders associated with loss of the nerve fibre layer. Rake and wedge defects and diffuse nerve fibre changes are demonstrated in cone-rod dystrophies, rod-cone dystrophies (retinitis pigmentosa), juvenile macular degeneration, fundus flavimaculatus (Stargardt's disease), vitelliform macular dystrophy, and Leber's congenital amaurosis.

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Subjects and materials

Patients with various types of retinal degeneration who clearly showed nerve fibre loss were selected from our files. In each case the diagnosis was made after a careful medical and family history and ophthalmic examination consisting of external and slit-lamp examination and direct and indirect ophthalmoscopy. In selected cases fluorescein angiography, electroretinography (ERG), electrooculography (EOG), and dark adaptometry by standardised techniques were performed.[6 7] All the findings were analysed to arrive at the most accurate diagnosis. A summary of the diagnoses and pertinent clinical findings can be found in Table 1.

Results

Fig. 1A–H. Patients 1–8 with outer retinal layer disease. All show rake defects (dark striations within grey translucent areas of more normal retinal nerve fibre layer (some arrowed) in temporal arcades and loss of retinal nerve fibre layer detail in the papillomacular bundle. Defects are less distinct than on funduscopy, as the prints are copies of colour transparencies. The diagnoses of the patients are given under the individual Figs.

Patient 1. A 25-year-old male with vitelliform macular dystrophy had best corrected vision acuity of

Table 1 *Details of patients*

Patient	*Age*	*Diagnosis*	*Visual acuity*	*Electro-retinogram*	*Goldmann fields*
1	25	Vitelliform dystrophy	20/20 20/50	Normal	Minimal central depression OD; relative central and paracentral scotomata OS
2	26	Simplex cone-rod dystrophy	20/30 20/40	⅓ of normal, photopic worse affected	Baring of blindspot; partial ring scotoma superiorly, contracted OU
3	31	Dominant cone-rod dystrophy	20/200 20/100	Barely recordable	Pseudoaltitudinal defect OU
4	7	Juvenile Leber's congenital amaurosis	20/70 20/60	Unrecordable	Less than 10° to IV OU
5	22	Stargardt's disease	20/40 20/50	Normal	Full with central scotomata OU
6	33	Rod-cone dystrophy	20/20 20/30	Barely recordable	Small central fields with peripheral islands OU
7	7	Fundus flavimaculatus	20/80 OU	Normal	Normal
8	44	Choroideraemia (carrier)	20/30 OU	Borderline normal	Normal

20/20 in the right eye and 20/50 in the left (Fig. 1A). ERG and dark adaptation were within normal limits, though the cone portion of the dark adaptation curve was somewhat low. The EOG was abnormal, with light peak to dark trough (Lp/Dt) ratios of 1·2 on the right and 1·35 on the left.

Patient 2 was a 26-year-old woman with cone-rod degeneration. Her visual acuity was 20/30 on the right and 20/40 on the left (Fig. 1B). The ERG showed a barely recordable photopic response, one-third normal scotopic responses, and unrecordable flicker responses. Visual fields showed baring of the blind spot and partial ring scotomata (Figs. 2 and 3).

Patient 3 was a 31-year-old woman with cone-rod degeneration of the autosomal dominant type. She had a visual acuity of 20/200 on the right and 20/100 on the left (Fig. 1C). The photopic ERG was barely recordable, the scotopic ERG one-half normal. Visual fields showed pseudoaltitudinal defects with smaller isoptres in the right eye (Fig. 4).

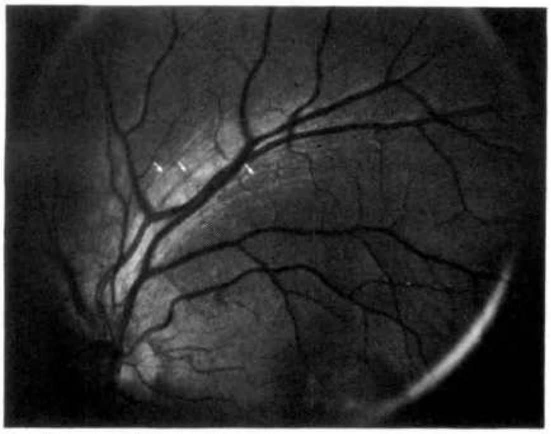

Fig. 1A *Vitelliform dystrophy.*

Patient 4 was a 7-year-old with juvenile Leber's amaurosis.[8] Visual acuity was 20/70 on the right and 20/60 on the left (Fig. 1D). The ERG was unrecordable. The Goldmann field was less than 10° to a I-4 target.

Patient 5 was a 22-year-old male with fundus flavimaculatus (Fig. 1E). Visual acuity was 20/40 on the right and 20/50 on the left. The ERG was normal. The EOG showed 155% rise. Visual fields were full, with central scotomata.

Patient 6 was a 33-year-old man with rod-cone degeneration (Fig. 1F). Visual acuity was 20/20 on the right and 20/30 on the left. The photopic and

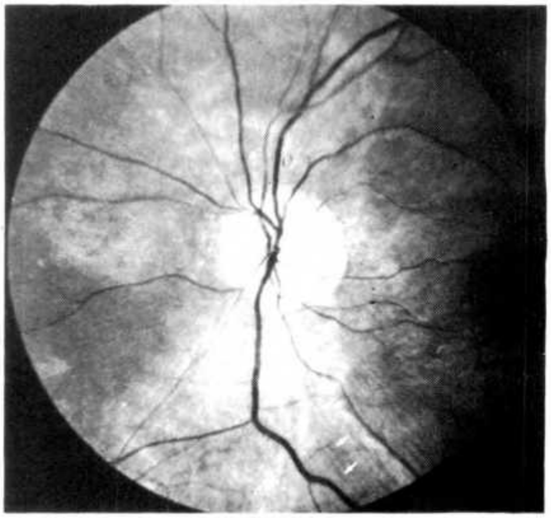

Fig. 1B *Cone-rod dystrophy.*

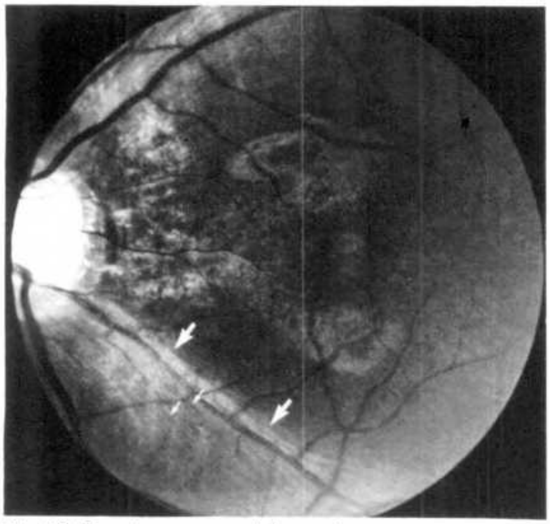

Fig. 1C *Dominant cone-rod dystrophy.*

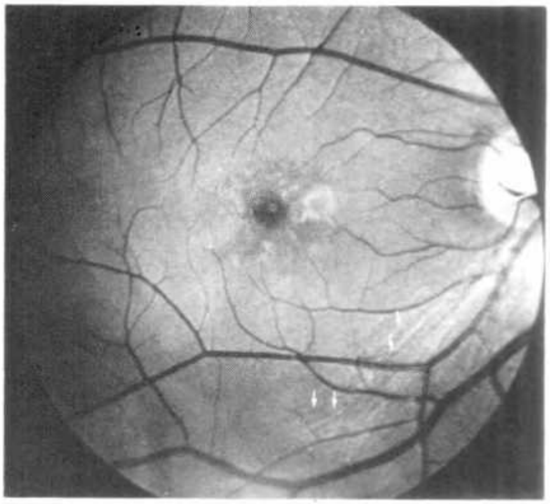

Fig. 1E *Stargardt's dystrophy.*

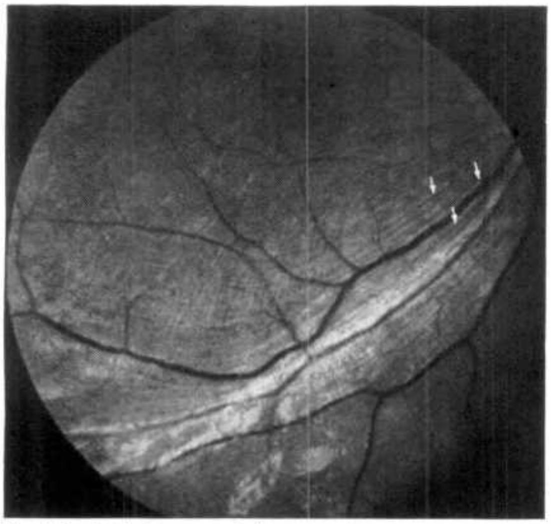

Fig. 1D *Leber's congenital amaurosis.*

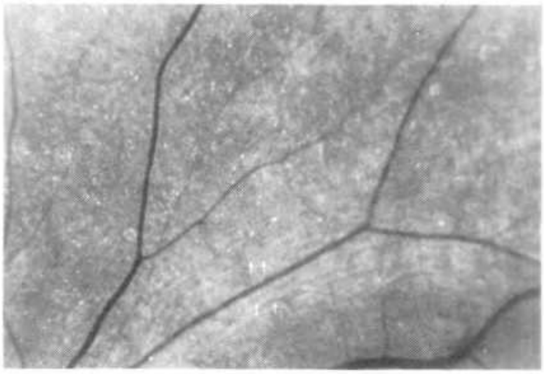

Fig. 1F *Rod-cone dystrophy.*

scotopic ERGs were barely recordable. Dark adaptation was 4·25 log units elevated at 40 minutes. The visual field showed small central fields with very large ring scotomata and large peripheral islands (Fig. 5).

Patient 7 was a 7-year-old girl with fundus flavimaculatus (Fig. 1G). Visual acuity was 20/80 OU. The ERGs were normal bilaterally, as were the Goldmann fields.

Patient 8 was a 44-year-old woman who was a carrier of choroideraemia (Fig. 1H). Visual acuity was 20/30 in each eye. The photopic ERG was borderline and the scotopic ERG normal on the right and borderline on the left. The dark adaptation was 1·9 log units elevated at 40 minutes. Visual fields were normal.

Discussion

We present eight examples of atrophy of the retinal nerve fibre layer in patients with outer retinal layer diseases. These changes are very frequently present when sought but may be difficult to detect against a background of generalised atrophy of the nerve fibre layer and/or retinal pigment epithelium and other pigmentary aberrations. In general the changes in the nerve fibre layer correlate well with the severity of the disease process. However, it is often difficult to link individual nerve fibre layer defects with specific field defects where there are also field defects due to the basic outer retinal layer disease process. Once nerve fibre layer atrophy appears, its progression

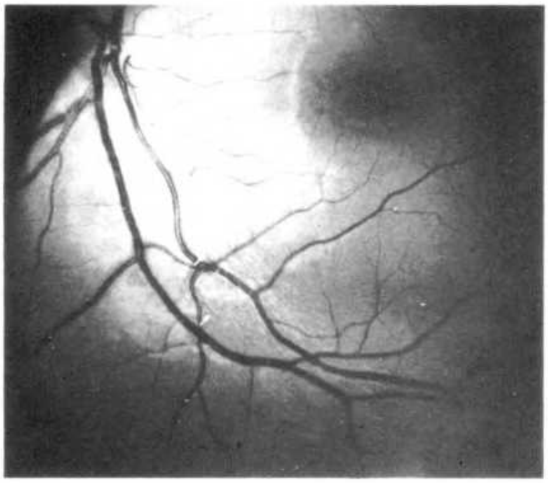

Fig. 1G *Fundus flavimaculatus*.

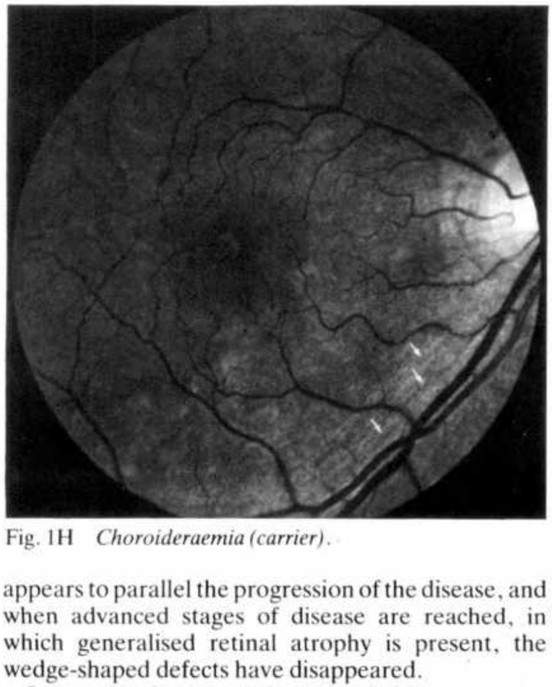

Fig. 1H *Choroideraemia (carrier)*.

appears to parallel the progression of the disease, and when advanced stages of disease are reached, in which generalised retinal atrophy is present, the wedge-shaped defects have disappeared.

In previously reported cases of damage to the retinal nerve fibre layer the primary insult has been to the optic nerve or another portion of the ganglion cell axon, such as the chiasm. The consequent changes in the nerve fibre layer represent direct injury to that axon, not evidence of remote effects or transsynaptic degeneration.

Thus the discovery of changes in the nerve fibre layer in disorders of the outer retinal layer raises important questions about the pathogenesis of these changes. Is there transsynaptic degeneration, or do

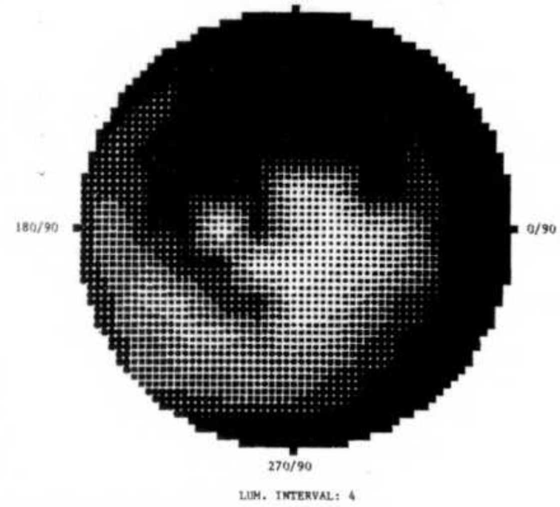

Fig. 2 *Visual field of patient 2 (Octopus)*.

these diseases of outer retinal layers actually directly involve the inner retinal layers as well?

Transsynaptic degeneration has been thought to occur only rarely and to minor degrees in adult humans or animals.[9] For this reason Hoyt and associates were able to point out the significance of one pattern of nerve fibre layer change (homonymous hemianopic hypoplasia) as indicative of congenital or very early injury to the postgeniculate central nervous system.[10]

If the diseases in question truly affect the outer retinal layers predominantly, then an explanation is needed for transsynaptic degeneration occurring after infancy.

Studies in monkeys confirm the clinical impression that transsynaptic degeneration is rare (or hard to detect) in the central nervous system of mature animals. Ablation of the striate cortex of immature monkeys produces approximately 70% loss of retinal ganglion cells,[11] much less ganglion cell loss in adult animals.[12]

However, some retrograde transsynaptic degeneration does occur in adult monkeys. Dineen *et al.* ablated the striate cortex of adult monkeys and found a 30% loss of parafoveal retinal ganglion cells.[12] In addition physiological evidence of transsynaptic transport of neural materials[13] might provide a logical mechanism by which transsynaptic effects are mediated in adult animals.

INVOLVEMENT OF OUTER RETINAL LAYERS

Electrophysiological studies suggest that some diseases generally considered to affect predominantly inner or outer retinal layers, but not both,

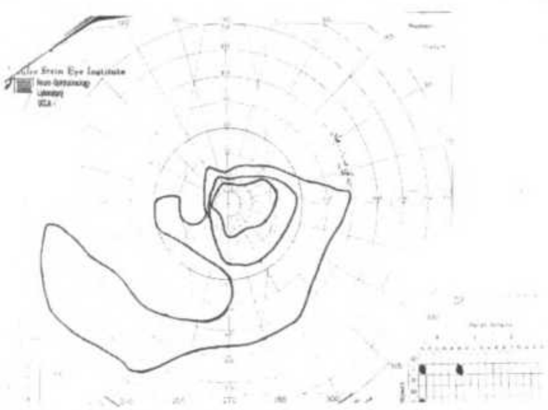

Fig. 3 *Visual field of patient 2.*

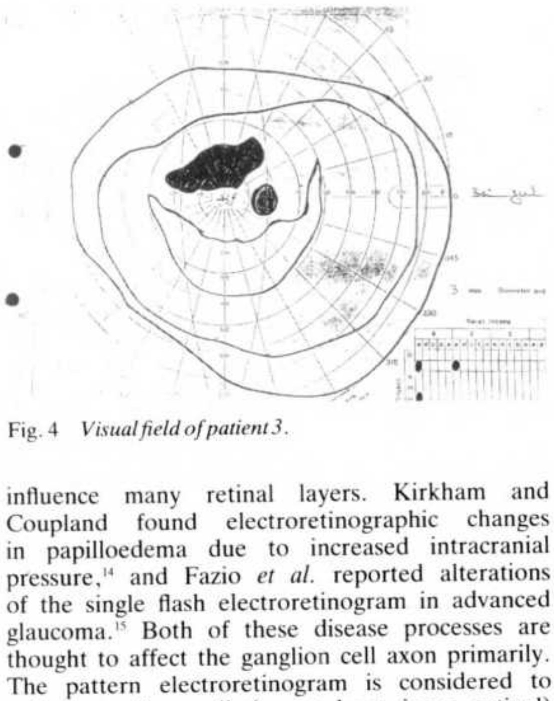

Fig. 4 *Visual field of patient 3.*

influence many retinal layers. Kirkham and Coupland found electroretinographic changes in papilloedema due to increased intracranial pressure,[14] and Fazio *et al.* reported alterations of the single flash electroretinogram in advanced glaucoma.[15] Both of these disease processes are thought to affect the ganglion cell axon primarily. The pattern electroretinogram is considered to reflect ganglion cell (or at least inner retinal) activity,[16] but it is significantly diminished in Stargardt's disease, an outer retinal layer process[17] (and Newman NM, Jackson JL, Latner B, personal communication).

Other aberrations of the ganglion cell axon are not uncommon in diseases of the outer retina. Clinically, waxy pallor of the optic disc has long been recognised as a sign in advanced rod-cone dystrophies, but neural atrophy has gone unnoted and is not discussed as a pathological feature of outer retinal layer disease.[18,19] Unusual drusen also are noted in retinitis pigmentosa, frequently occurring in the nerve fibre layer away from the disc substance, in contrast to optic nerve head drusen which are confined to the papilla.[20] In addition the temporal portion of the disc and its nerve fibre layer appear to be severely diminished or missing in patients with *X*-linked congenital stationary night blindness,[21] and similar changes and telangiectasis are extremely common in the cone-rod degenerations.[22]

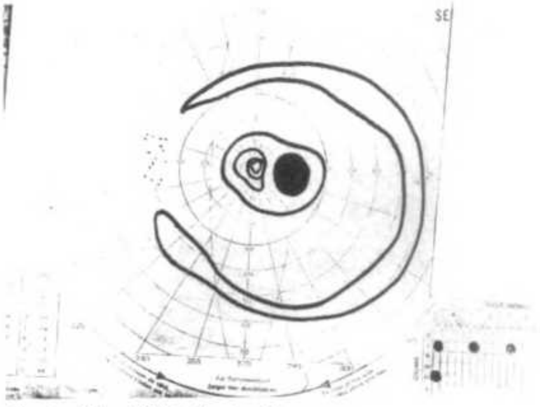

Fig. 5 *Visual field of patient 6.*

Thus substantial anatomical, physiological, electrophysiological, and clinical evidence indicates nerve fibre layer involvement in outer retinal layer disease and is consistent with our observations of atrophic nerve fibre layer changes.

The observed changes appear to be signs of disease processes initiated in early, even prenatal, development because many of the changes we illustrate are found in children. Early outer retinal damage may cause transsynaptic changes. In primate studies on the retinal degeneration from striate cortex lesions the severity of transsynaptic degeneration was directly related both to age and to time[23]—for example, the younger the animal and the longer the observation period following the injury, the greater the degeneration. Alternatively, some of the mentioned disease processes may involve metabolic and physiological changes which occur in many retinal layers but appear clinically as changes in the outer retinal layers predominantly.

Awareness of the occurrence of these changes in the nerve fibre layer in outer retinal layer disease has at least one practical implication. The presence of nerve fibre layer changes not readily explained by optic nerve disease should prompt examination of the patient for diseases of the outer retinal layer.

This project was supported in part by Research to Prevent Blindness, Inc., and a centre grant from the National Retinitis Pigmentosa Foundation.

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Viscoelastic evacuation of traumatic hyphaema

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SUMMARY A technique for the safe evacuation of traumatic hyphaema is described. The viscoelastic properties of Healonid are used to separate the hyphaema from other ocular tissues and to extrude it through a small corneal incision. Healonid maintains a deep anterior chamber and a stable intraocular pressure. It also protects the lens, cornea, and iris and allows clear observation.

Surgical evacuation of a hyphaema becomes necessary when it is the cause of a prolonged rise in intraocular pressure, when there is a danger of blood staining of the cornea, and when a clot is likely to undergo fibrosis.

Removal of a hyphaema is often a difficult and risky procedure. It may not be possible to remove a clot unless a very large incision is made. It may not be possible to separate the clot from the iris or chamber angle. Sudden reduction of the intraocular pressure may cause further bleeding and a cycle of bleeding, glaucoma, evacuation, and further bleeding. Poor observation and a collapsed anterior chamber make manipulation within the eye dangerous and promote injury to the cornea, iris, and lens. A large incision may cause prolapse of iris, ciliary body, or lens.

The technique to be described makes use of the viscoelastic properties of Healonid (sodium hyaluronate)–its abilities to separate tissues and maintain space–and is considered to be an improvement on that of Miller and Stegmann.[1] It requires only small incisions, separates and removes clots completely, maintains the intraocular pressure, reduces the likelihood of further bleeding, maintains a deep anterior chamber, and allows clear observation, thus offering protection to the iris and lens and safe surgical manipulation within the eye.

Material and method

1. A 1 mm stab incision is made with a keratome shaped diamond knife on the corneal side of the limbus. This opening is used for the injection of Healonid. The opening is better made on the side to suit the surgeon's master hand.

2. A similar sized incision is made on the opposite side of the cornea if the hyphaema is fluid. When the hyphaema is clotted, this incision is enlarged to 3 mm (Fig. 1).

3. Healonid is injected through a fine cannula. Begin close to the internal opening of the incision. The hyphaema is pushed towards the other side. Angle the cannula up and down to clear all of the hyphaema from the region around the stab opening. If the injection is made slowly, there is no mixing between the Healonid and blood (Fig. 2).

4. The intraocular pressure will begin to rise as Healonid is injected. The injection is therefore accompanied by opening of the incision on the opposite side—gentle pressure with an iris spatula on the limbal side of the incision. Blood will begin to extrude, and the pressure will remain constant.

5. The Healonid cannula is gradually advanced across the anterior chamber. Clots are separated from the iris or angle by directing flow toward the appropriate position (Fig. 3).

6. Perfect visibility through the Healonid allows clear observation of the iris and lens and of the depth

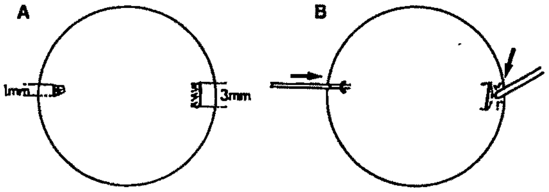

Fig. 1 A: *1 and 3 mm incisions are first made on opposite sides of the cornea.* B: *Healonid is injected through the 1 mm incision. The hyphaema is evacuated and the ocular pressure regulated by depressing the limbal edge of the 3 mm incision.*

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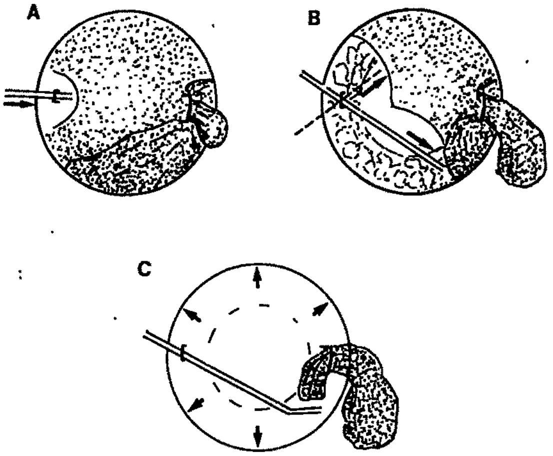

Fig. 2 A: *Healonid is injected slowly into the anterior chamber.* B: *The cannula is advanced and angled appropriately.* C: *Healonid remains in the anterior chamber after evacuation of the clot, thus maintaining the ocular pressure.*

of the anterior chamber. The cannula can therefore be manipulated inside the eye with safety (Fig. 3).

7. The Healonid is left in the anterior chamber once the hyphaema has been removed. The cornea is sutured if necessary.

8. Postoperative control of the intraocular pressure is achieved by the use of oral acetazolamide or topical timolol drops.

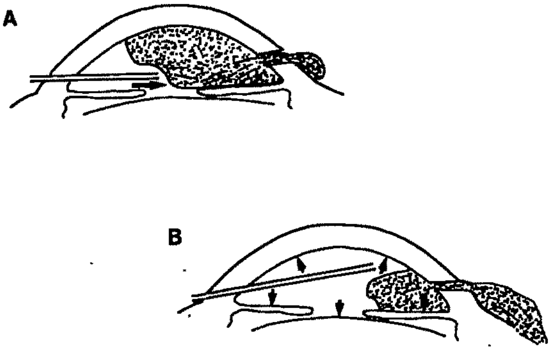

Fig. 3 A: *The cannula and Healonid injection are directed so as to separate the hyphaema from the iris and lens.* B: *The Healonid maintains a deep anterior chamber, giving protection to the lens, iris, and cornea.*

Discussion

This technique has been used successfully on a small number of patients. It offers advantages over other methods. The necessary incisions into the cornea are small and may not require sutures, in contrast to the large 180° incision often advocated. The hyphaema, clotted or fluid, is readily separated from other intraocular structures and extrudes through the small exit wound. It is difficult to separate a clot from the iris or angle with any other instrument without causing direct tissue damage. The intraocular pressure can be kept stable by controlling the rate of Healonid injection and blood/aqueous extrusion. The sudden fall of the intraocular pressure to zero which must occur after any large incision, and which is probably a major factor in causing a second haemorrhage, is thus avoided. The anterior chamber is maintained throughout by injecting Healonid into an intermittently closed system. The Healonid-filled part of the chamber allows perfect observation while protecting the cornea, iris, and lens.

All manipulations within the eye are therefore made under direct observation in a deep and stable chamber. The danger of instrumental injury to the lens in particular, and the iris and cornea is thus greatly reduced.

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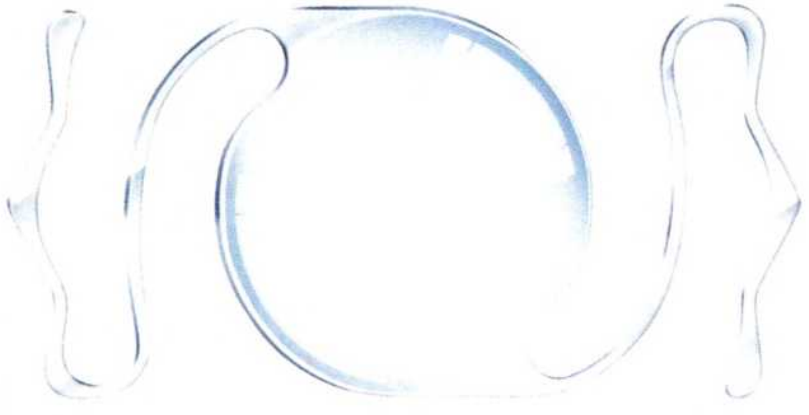

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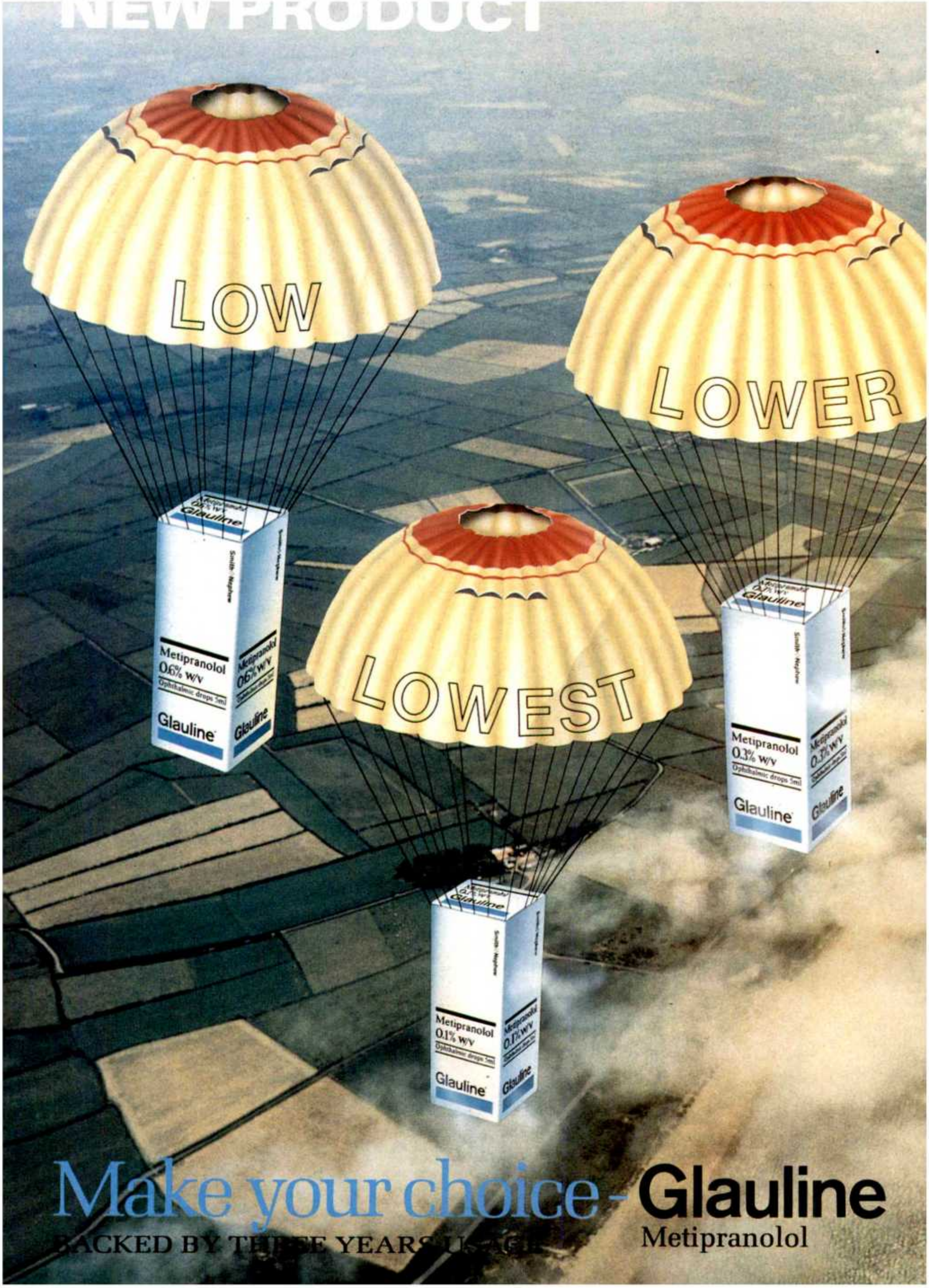
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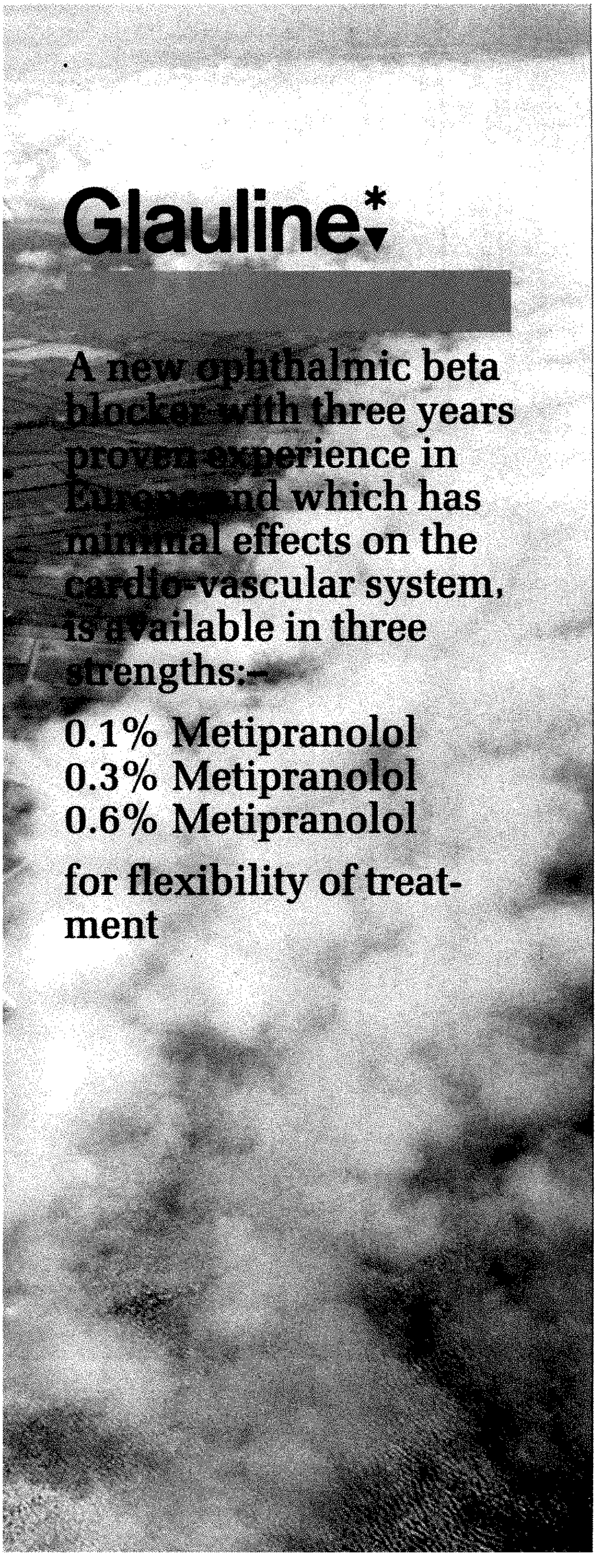

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or other untoward reactions occur, discontinue the medication. **Precautions** Patients with histories of herpes simplex keratitis
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British Journal of Ophthalmology, 1987, **71**, 29–31

A corneal abnormality associated with trisomy 8 mosaicism syndrome

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SUMMARY Eye abnormalities are a significant feature of trisomy 8 mosaicism syndrome. This paper gives the first account of the specific histopathology of a corneal opacity which is characteristic of this syndrome. The importance of early recognition is stressed because of potential therapeutic visual improvement. The necessity of including mosaic trisomy 8 in the differential diagnosis of such corneal opacities is illustrated by this case.

The trisomy 8 mosaicism syndrome is now recognised as having distinct clinical features which include mild to moderate mental retardation, characteristic facies and ears, and orthopaedic, cardiovascular, and genitourinary abnormalities.[1-3] Characteristic dermatoglyphic patterns have also been described.[1-5] We report a case of a dense corneal opacity associated with the syndrome and offer some suggestions for management of the patient with such a lesion.

Case report

The patient was the first male child of unrelated Caucasian parents. The mother was aged 31 years and the father 28 years at the time of the birth. The mother had a normal daughter from a previous marriage.

A paediatrician (DWG) was consulted at birth because of unusual dysmorphic features which included frontal bossing, upturned nose, thick lips, and prominent ears with hypertrophic antihelices. These features are shown in Fig. 1 and 2 taken at 5 months of age prior to eye surgery. Chromosome studies confirmed the presence of trisomy 8 mosaicism (46,XY/47,XY, +8) in the child, while those of the parents were normal.

Ophthalmological findings were a dense opacity of the right cornea (Fig. 1) obscuring the pupil, and a divergent squint and bilateral nasolacrimal duct obstruction. At the age of 5 months an electroretinogram performed under general anaesthetic showed a normal response to 40 check stimulus in the left eye but no response in the right. Flash stimuli resulted in a normal identical response from each eye. These

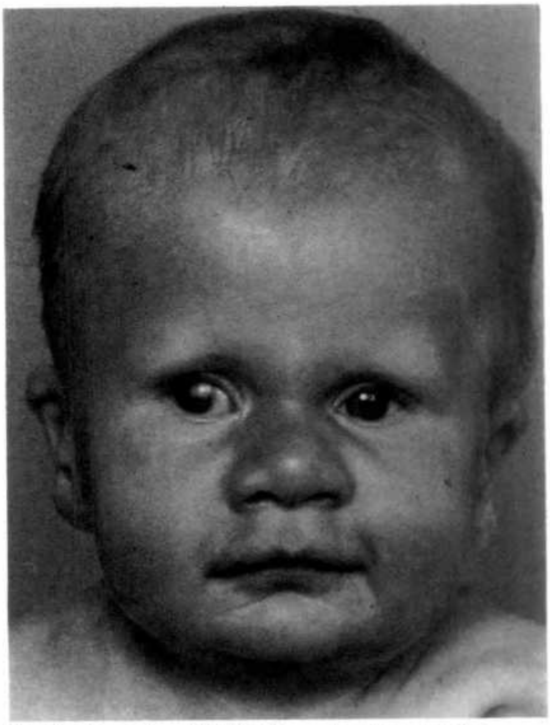

Fig. 1 *Front view of child at 5 months of age showing characteristic facies and ears with the dense corneal opacity present in the right eye.*

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results confirmed the integrity of the visual pathway but reduced vision in the right eye consistent with amblyopia.

The lesion was subsequently removed and penetrating keratoplasty performed. The pathologist reported a 'cream white tissue flake with some evidence of surface pigmentation while microscopy showed a dense plaque of richly vascularized fibrous tissue apparently of congenital origin' (Fig. 3).

Three months postoperatively the cornea remained clear. Although a right divergent squint was still present, the patient could fixate well with the right eye when the left was occluded. Further occlusion was deemed necessary to help overcome residual amblyopia.

Discussion

About 70 cases of trisomy 8 mosaicism have now been reported.[3] The syndrome is distinguished by its characteristic facies, distinctive toe posture, absent or dysplastic patellae, joint contractures, and palmar or plantar furrows. Mental retardation is an almost uniform finding.[3]

Ocular manifestations are common in the syndrome, with strabismus occurring in almost half of the described cases.[1-3 5 6] Deep set eyes have also been reported.[7] A congenital cataract and retrolental fibroplasia were noted in another child but were related to oxygen therapy for respiratory distress in the neonatal period.[8]

The present report describes a corneal opacity similar in appearance to those previously described,[1 2 9] but the pathology of these lesions was not reported. Histologically the present lesion showed richly vascularised fibrous tissue. Corneal abnormalities are rare findings in children and the association with chromosomal disorders even rarer. Megalocornea has been described in Down's syndrome[10] and in association with multiple skeletal anomalies.[11]

Peters' anomaly (mesodermal dysgenesis of the cornea) is a rare developmental abnormality of the anterior segment of the eye and may present with congenital corneal opacities.[12 13] However, the lesion described in this paper was in the superficial layers of the cornea. Corneal opacities have also been described in other conditions,[7 14-16] but the appearance of the corneal lesion is again quite different.

We present the fourth report of a child with

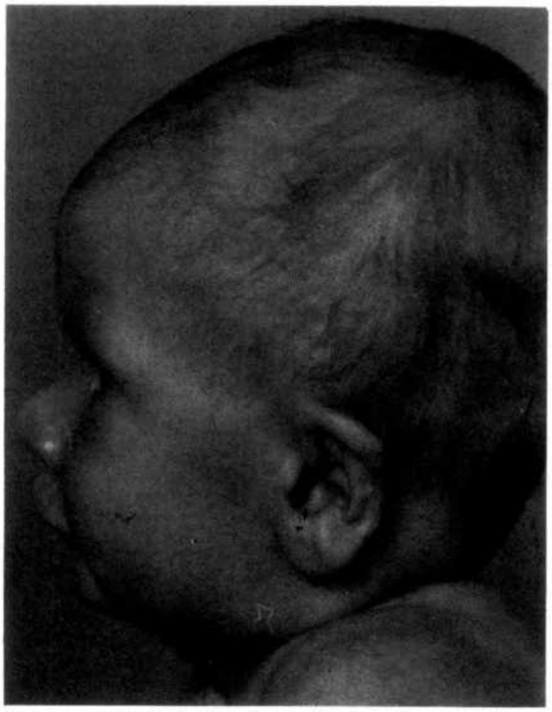

Fig. 2 *Side view of child at 5 months of age showing dysmorphic features, particularly of the ears.*

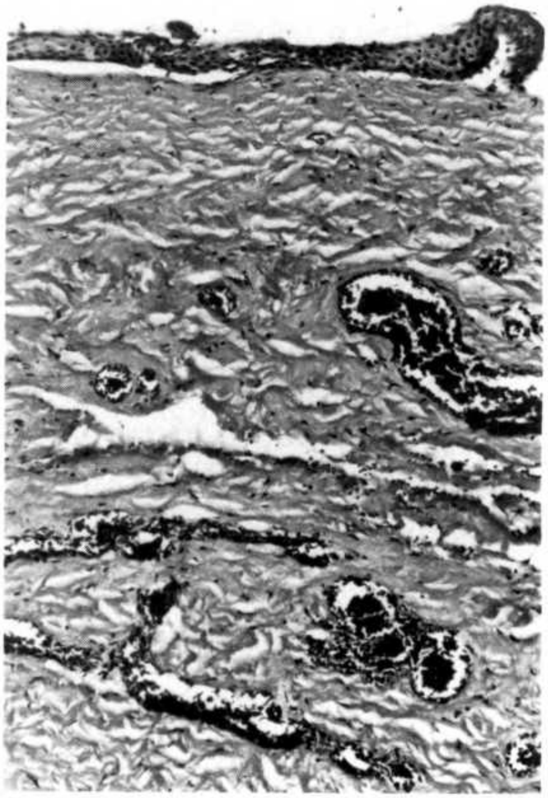

Fig. 3 *Histopathology of corneal opacity showing richly vascularised fibrous tissue in the superficial layers of the cornea.*

trisomy 8 mosaicism and a corneal opacity and the first histological examination of such a lesion. It was found to be not consistent with Peters' anomaly. By the age of 5 months the child was unable to fixate on objects owing to occlusion amblyopia even though he had a normal electroretinogram. To prevent the development of amblyopia, recognition and treatment of the lesion soon after birth is essential. Removal of the lesion and subsequent corneal grafting is considered to be the treatment of choice if the pupil is occluded. Keratoplasty in the first three months is advisable to prevent amblyopia. Microsurgical techniques[13] make this possible. Amblyopia may still be a problem owing to postoperative anisometropia but should respond to therapy. The latest report[9] described +4·5 D hypermetropia in both eyes with several dense stromal opacities in the right eye. Recurrent examinations under anaesthetic showed no change over 12 months. This lesion did not appear to be obstructing the pupil.

The pathogenesis of the lesions is unclear[9] but may represent areas of trisomic cells which have developed and then died, leading to scar formation.

Children with trisomy 8 mosaicism, although almost invariably mentally retarded, may have a life span of at least 20 years.[10] To keep their intellectual and visual sensory handicap to a minimum, early recognition and treatment of this lesion is essential.

We are grateful to the staff of the cytogenetics laboratory at the Mater Misericordiae Hospital, Brisbane, to Dr J Sullivan for reporting on the pathology, and to Mrs V L Hawkins and Mrs P B Carter for typing assistance.

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Primary orbital amyloidosis localised to an extraocular muscle

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SUMMARY Primary, localised orbital amyloidosis has been reported previously in only 15 patients. A case with amyloidosis strictly localised to an extraocular muscle is presented.

Ophthalmic involvement frequently occurs in generalised amyloidosis.[1 2] Localised orbital amyloidosis is very rare and has been reported in only 15 patients. A patient with amyloidosis strictly localised to an extraocular muscle is presented. This has not been previously reported.

Case report

For the last 10 years a 60-year-old woman had a tendency to diplopia when looking quickly to one side. In 1984 a clinical examination revealed a right exotropia, and a Lees screen showed reduced motility of her right eye, particularly a reduction of the adduction—that is, underaction of the medial rectus muscle. There was also a strong overaction of the lateral rectus muscle of the left eye. A forced duction test of the right eye revealed great resistance in both adduction and abduction. The patient had normal visual acuity and only a slight hypermetropia (+0·5 right and left eyes). Her fundi were normal and no visual field defects were noticed. Computed tomographic (CT) scanning showed a normal brain configuration, but in the right orbit the medial rectus muscle had a fusiform thickening, being three times as thick as the left medial rectus muscle (Figs. 1, 2). No infiltration or destruction of the surrounding structures was seen.

In January 1985 the patient underwent surgery for her right exotropia (resection of the right medial rectus muscle and recession of the right lateral rectus muscle, with a traction suture in adduction). A biopsy of her right medial rectus muscle was also

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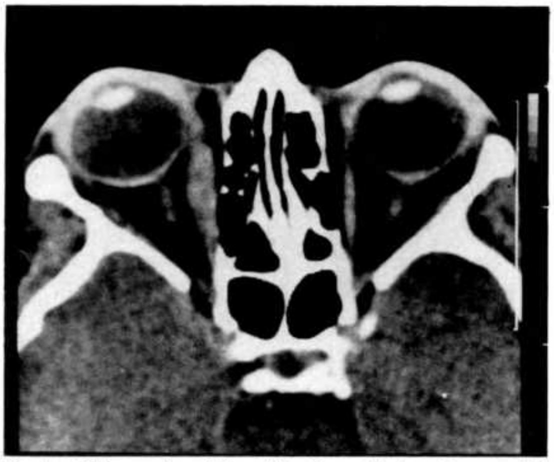

Fig. 1 *CT scanning of the orbits, 4 mm thick section parallel with the optic nerves.*

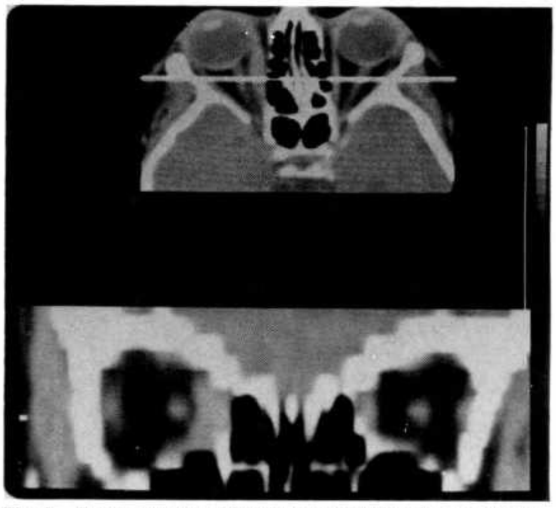

Fig. 2 *Reconstruction of sections retrobulbarly through the orbits, demonstrating the optic nerves and the extraocular muscles in frontal projection.*

performed. This muscle appeared waxy and showed ordinary muscle structure only in the 2 mm closest to its insertion. Pathological examination revealed an amorphous structure which, after staining with Congo red, showed a green birefringence. Only a few fragments of the ordinary muscle structure could be identified. The histopathological diagnosis was amyloidosis.

A pulmonary *x*-ray was normal. Phonocardiography and ultracardiography did not show any abnormality. Biopsies of the subcutaneous fat from the abdomen and the cheek showed no amyloid deposits. No proteinuria was found, and the results of serum and urine electrophoresis were normal. No rheumatoid factor or antibodies against cell nuclei, smooth muscle, glomeruli, and mitochondria could be found. There was therefore no sign of generalised amyloidosis.

In April 1985 the patient underwent supplementary surgery for a slight esotropia with intermittent diplopia (recession of the right medial rectus muscle with an adjustable suture). A CT scan in July 1985 showed the same picture as before.

The patient will be followed up with ophthalmic examinations, tests of visual fields, and CT scanning.

Discussion

Amyloid is an extracellular, proteinaceous material that can be deposited in various tissues. Histopathological identification is best made with Congo red staining. When viewed with a polarising microscope all forms of amyloid show a green birefringence.

Amyloidosis is the term for a heterogeneous group of diseases characterised by accumulation of amyloid in different tissues. It has been subjected to many classifications. A clinically widely used classification is: (1) primary generalised amyloidosis (without any underlying disease); (2) secondary amyloidosis (associated with, for example, chronic infection, rheumatoid arthritis); (3) amyloidosis associated with myelomatosis; and (4) tumour-forming amyloidosis, characterised by localised amyloid masses.[3] Some authors also note a fifth, hereditary, form of amyloidosis.[4] Analyses of the chemical structure of amyloid are now making new classifications possible.[5]

Ophthalmic involvement has been reported in all subgroups of amyloidosis described above.[4] The case presented here is of localised orbital amyloidosis. Apart from amyloid tumours of the conjunctiva and lid, localised orbital amyloidosis is rare,[1 2] and only 15 patients with primary localised orbital amyloidosis have been reported so far.[1 2 4 6-16] Four of the previously reported 15 cases were bilateral. Three patients had their lesions localised in the lacrimal gland. In most of the remaining patients the amyloid tumour extended deep and infiltrated the orbit. No case has previously been reported in which the amyloid tumour is localised only to an extraocular muscle.

In conclusion, localised orbital amyloidosis seems to be rare. This is the first case reported with amyloid entirely localised to an extraocular muscle.

Dr A Moberg, Department of Pathology, Danderyds Hospital, kindly helped with the histopathological investigation.

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Anterior uveal neurilemmoma—a rare neoplasm simulating malignant melanoma

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SUMMARY A 30-year-old woman presented with dilated episcleral vessels in the right eye which were found to be associated with an underlying ciliary body tumour. Contact lens examination, transpupillary transillumination, ultrasonography, computerised tomography, magnetic resonance imaging, and fine needle aspiration biopsy produced apparently conflicting and inconclusive results, and the eye was enucleated. Light and electron microscopy showed the lesion to be a neurilemmoma (schwannoma), of which very few cases have been reported. The clinical and pathological features are described and discussed.

Intraocular, benign, peripheral nerve neoplasms are rare. Shields *et al.*[1] listed 18 tumours occurring in 17 patients, only two of whom had associated neurofibromatosis. Only four of these tumours were in the ciliary body; three were described as neurilemmomas, the other as a neurofibroma. More recently Rosso *et al.*[2] have added a further case. We describe an additional case which caused diagnostic difficulties despite the use of modern ancillary investigations. The correct diagnosis became apparent only after examination of the enucleated eye.

Clinical history

A 30-year-old Caucasian woman presented in September 1985 with a two months' history of gradual deterioration of vision in the right eye. She also had prominent episcleral vessels which she had first noticed five years previously in the same eye. Her general health was good and there was no relevant family history of ocular or systemic disease.

On examination the vision in the right eye was found to be reduced to 6/12, with correction, as a result of localised lens opacification, subluxation, and indentation by a large inferonasal ciliary body tumour (Fig. 1a). The tumour appeared pigmented and solid on ophthalmoscopic examination and was related to the overlying dilated episcleral blood vessels. Gonioscopy showed narrowing of the angle inferonasally but the appearance was otherwise normal. The intraocular pressure, pupillary reactions, and remainder of the anterior and posterior segments of the eye were normal. The left eye was healthy, with an uncorrected visual acuity of 6/5. No abnormalities were found on general physical examination.

The tumour transilluminated brightly. Ultrasonography suggested that it was cystic in nature. Computerised tomography, however, suggested that the lesion was solid (Fig. 1b); there was no response to intravenous contrast medium. Fine needle aspiration biopsy was performed on 19 September 1985

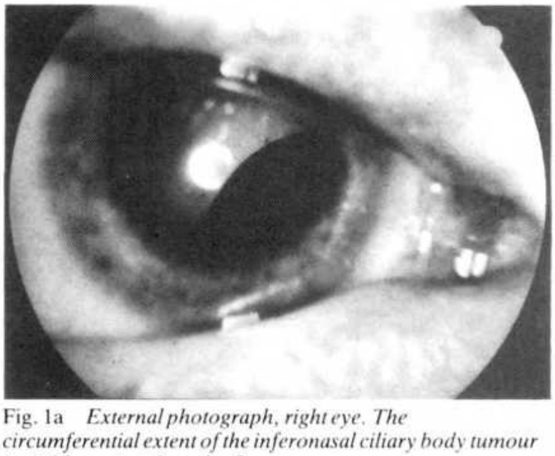

Fig. 1a *External photograph, right eye. The circumferential extent of the inferonasal ciliary body tumour is visible against the red reflex.*

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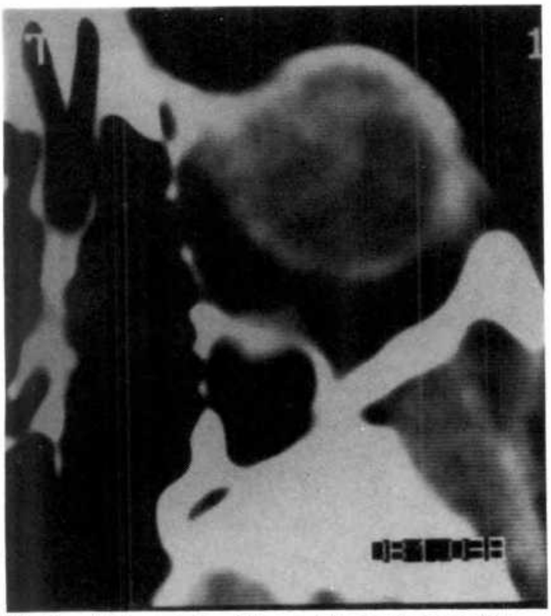

Fig. 1b *High resolution CT scan. The consistency of the tumour tissue was described as being identical to that of brain.*

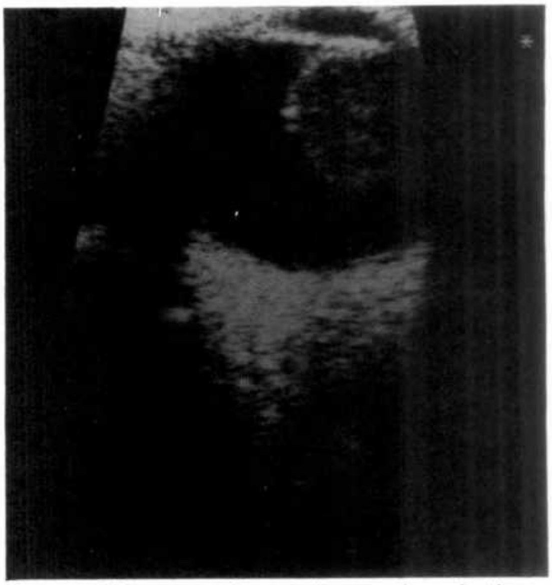

Fig. 1c *Oblique sector ultrasound scan performed with a 10 MHz contact probe, showing solid nature and posterior extent of tumour, as well as posterior indentation of lens. Because of the anterior location of the lesion, the base is poorly defined.*

beneath an inferonasal lamellar scleral flap, but the findings were equivocal (see below).

Subsequently the patient was referred to the Tennent Institute for further investigation and treatment. The above findings were confirmed except that ultrasound examination was suggestive of a solid lesion (Fig. 1c) of approximate dimensions 17 mm anteroposteriorly ×11 mm wide. Magnetic resonance imaging suggested a lesion of similar dimensions, but whether it was a solid tumour or a cyst containing proteinaceous fluid could not be determined (Fig. 1d). On angiography the lesion was completely non-fluorescent. The ^{32}P test was not performed. Excision biopsy was considered inappropriate, mainly because of the large size of the tumour, which involved more than one-third of the ciliary body. The eye was enucleated on 11 October 1985 because the tumour was increasing in size and because malignant melanoma could not be excluded.

Materials and methods

An air dried smear of the material obtained by fine needle aspiration biopsy was prepared and stained by the Giemsa technique.

After enucleation the globe was fixed in cacodylate buffered 3% glutaraldehyde for 24 hours, then sectioned obliquely (45°) and examined under saline with a dissecting microscope. A block including the pupil and optic nerve was prepared, embedded in paraffin wax, and sectioned by routine techniques. Sections were stained with haematoxylin and eosin (H and E) and by the diastase/periodic acid-Schiff, Loyez, Bodian, and Perls' techniques.

For transmission electron microscopy small pieces of tumour were postfixed in 1% osmium tetroxide in cacodylate buffer, dehydrated through graded

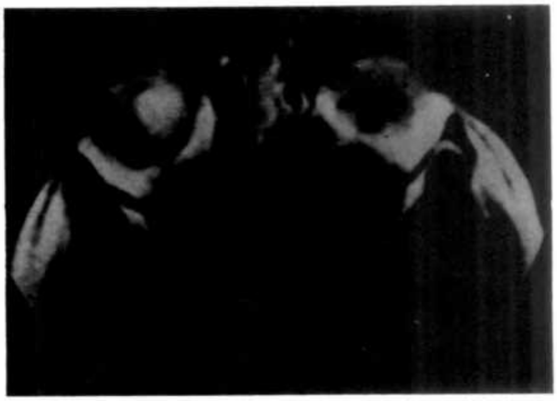

Fig. 1d *Magnetic resonance imaging. Axial view. SE40 sequence with TR:570MS; TE80MS performed on 0·15 T resistive magnet (Picker International) using a surface coil prototype. This demonstrates a well defined lesion giving a high signal.*

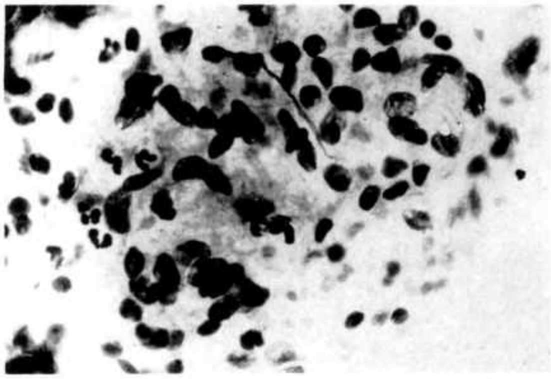

Fig. 2 *Fine needle aspirate, Giemsa stain. Loosely adherent tumour cells, in a fibrillary background, showing only minor nuclear abnormalities. No pigment is present.*

alcohols, and embedded in epoxy resin (Araldite). Ultrathin sections were cut, stained with uranyl acetate and lead citrate, and examined with a Philips 301 electron microscope.

Results

FINE NEEDLE ASPIRATION BIOPSY

The smear showed a fibrillary background containing loosely adhering cells of monomorphic appearance with ill defined cytoplasm and cell borders, mild nuclear pleomorphism, and some irregularity of chromatin distribution (Fig. 2). Nucleoli were inconspicuous, and no mitoses were seen. No pigment was noted.

No definite diagnosis was made in either centre where the smears were examined. It was thought that the lesion was a solid tumour and that malignant melanoma could not be excluded.

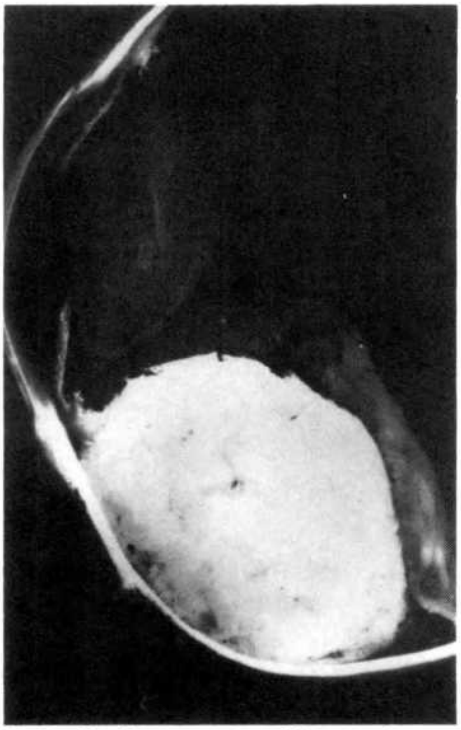

Fig. 3 *Enucleation specimen. Macroscopic photograph.*

ENUCLEATED EYE

Macroscopic findings. The globe measured 23×24×23 mm. Transillumination revealed a shadow in the inferonasal region. On oblique sectioning there was a rounded tumour mass measuring 15 mm anteroposteriorly × 11 mm high × approximately 15 mm wide, in the inferonasal region extending from the ciliary body to behind the equator (Fig. 3). It was white in colour and soft and homogeneous in texture. On transillumination at this stage the tumour showed unusual hyperlucency. The remainder of the eye appeared normal.

Light microscopy. The tumour formed a rounded mass distorting the ciliary body. It consisted of spindle cells with palely eosinophilic cytoplasm, in a finely fibrillary background. The nuclei showed finely dispersed chromatin and inconspicuous nucleoli, though there was some (generally mild) variation in nuclear size and shape. Groups of cells formed bundles and whorls, with some areas showing ill defined nuclear palisading, though this feature was not prominent (Fig. 4). Other areas showed loosely arranged cells and appeared microcystic (Fig. 5). The appearances were consistent with Antoni A and B areas of a neurilemmoma. Occasional bundles of myelinated nerve fibres were identified at the periphery of the tumour (Fig. 6). No features suggesting malignancy were present; mitotic figures were very rare and no areas of tumour necrosis or haemorrhage were seen. Occasional small foci within the tumour were rich in fine vascular channels.

Electron microscopy. The tumour cells from the cellular areas showed ovoid, sometimes multiple nuclei with clumping of the nuclear chromatin. The cells were surrounded by uninterrupted basement membrane material including collagen fibres (Fig. 7). Long-spacing collagen was noted in the basement membrane with a periodicity of 100–120 nm ('Luse bodies') (Fig. 7). Cytoplasmic processes showed intercytoplasmic interdigitations with pseudomesaxon formation (Fig. 8). A few poorly developed intercellular junctions were present. The cytoplasm of the tumour cells contained scattered mitochondria as well as Golgi complexes, short segments of rough endoplasmic reticulum, free ribosomes, and

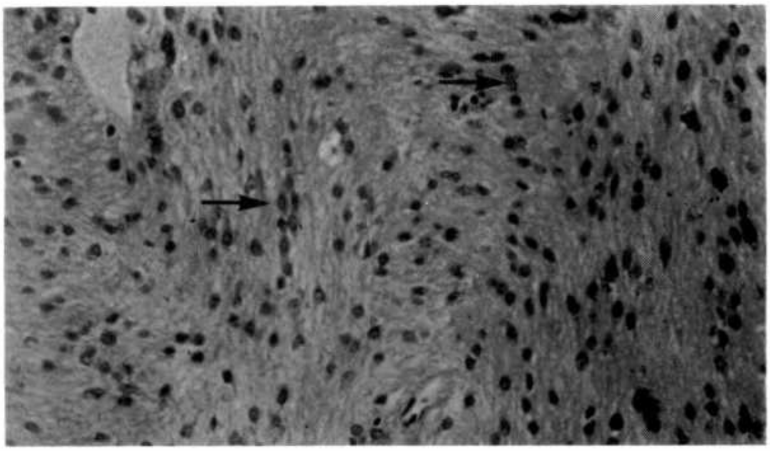

Fig. 4 *'Antoni A' area. Tumour cells in a fibrillary background. Ill defined nuclear palisades are arrowed. (H and E).*

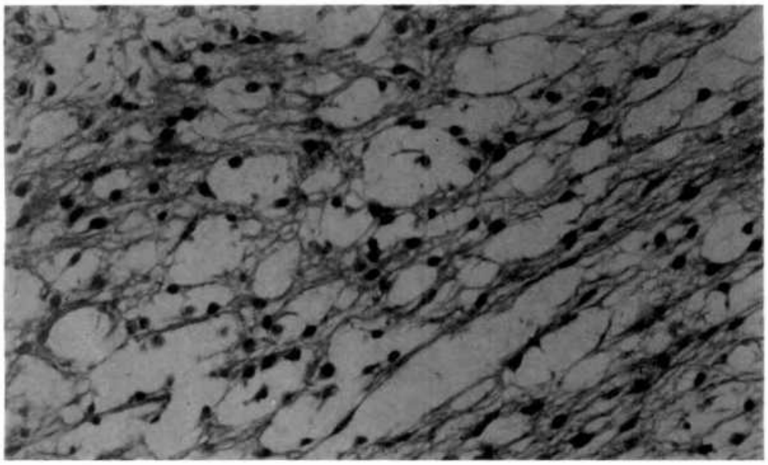

Fig. 5 *'Antoni B' area. Tumour cells are more widely spaced and the tissue appears microcystic. (H and E).*

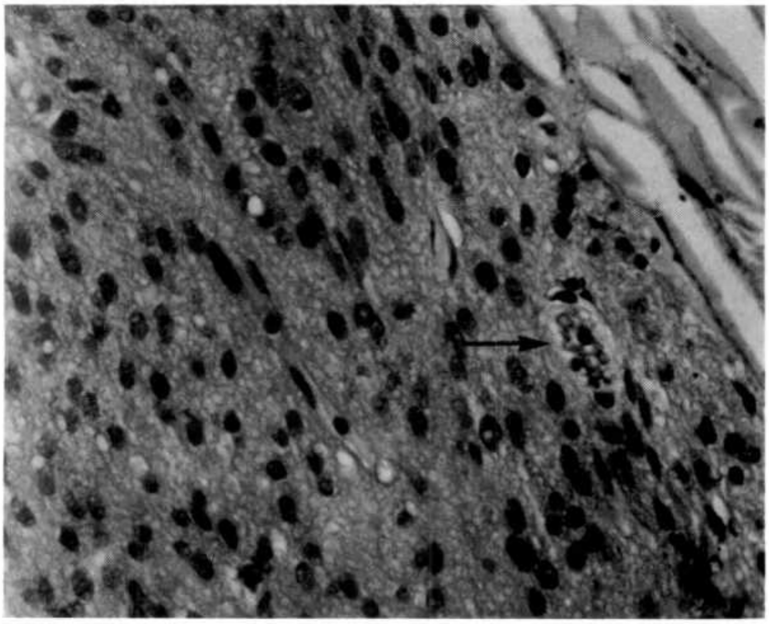

Fig. 6 *A myelinated peripheral nerve bundle (arrowed) is present at the edge of the tumour. Scleral connective tissue is also seen (top right of field). (H and E).*

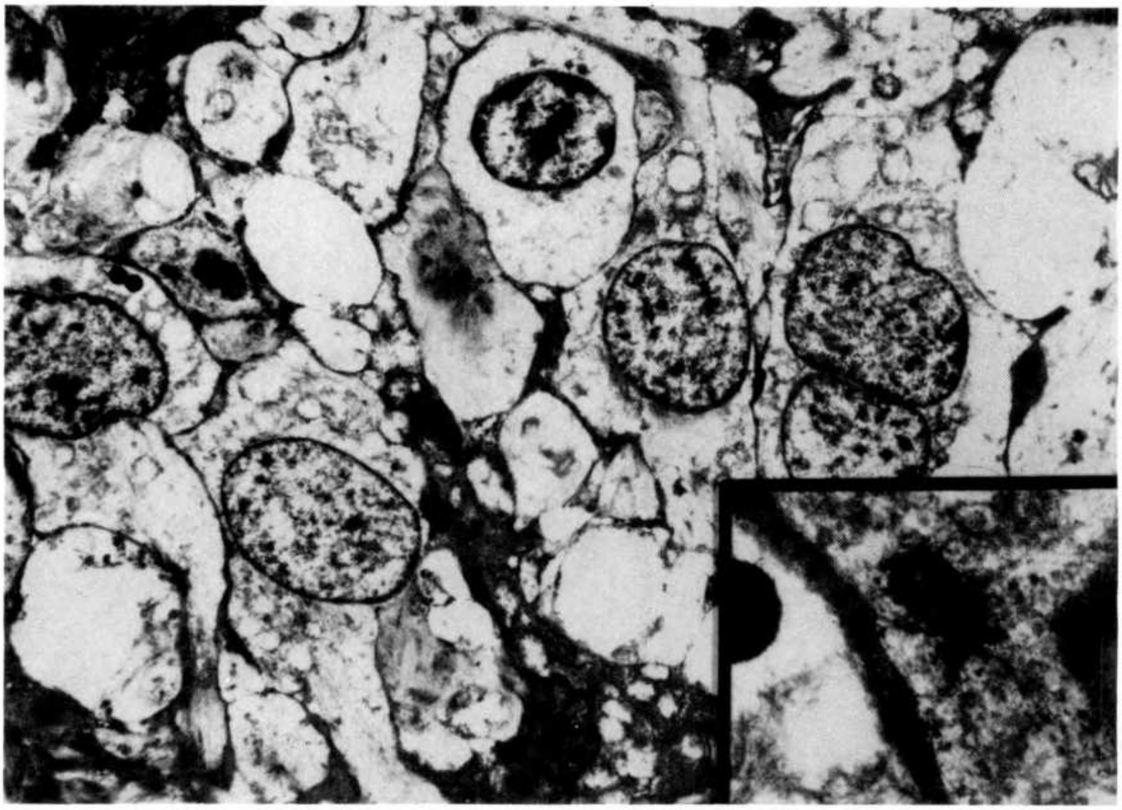

Fig. 7 *Electron micrograph. Tumour cells are covered by uninterrupted basement membrane and scattered collagen fibres. Long spacing collagen in the basement membrane is shown in the inset. (×1900; inset ×19 000).*

lysosome-like dense bodies. A few cells contained membrane bound vesicles, some of which contained electron dense material, possibly melanosomes and melanophagosomes.

In the less cellular areas there were occasionally lipid vacuoles within the cells, which were also surrounded by the basement membrane material. One cell showed a cilium which was seen lying in a vacuole. Pinocytotic vesicles and intracytoplasmic filaments were frequently found in the cytoplasmic processes.

Discussion

We have established the diagnosis of neurilemmoma (schwannoma) in this case by both light and electron microscopy.[3,4] No unusual features were seen by light microscopy, and the ultrastructural features of extensive basement membrane formation and pseudomesaxons are characteristic of neurilemmoma and not melanoma. Further, the presence of premelanosomes would not be diagnostic of melanoma, as they may be seen in pigmented neurilemmoma.[4] The interest of the tumour, therefore, lies in its rare occurrence in the anterior uvea.

While the term ciliary body neurilemmoma reasonably describes the clinical presentation of this and other reported cases, it is unsatisfactory as a pathological description. The presumptive structure of origin of the tumour is a ciliary nerve. On the basis of published descriptions the tumour described by Callender and Thigpen[5] appears the most likely actually to have arisen in the ciliary body. Two of the descriptions[2,6] do not include an illustration of the gross specimen or a low power photomicrograph. In our case, and that of Hogan and Zimmerman[7] and that of Donovan,[8] the tumour could have arisen from a ciliary nerve in the uveal tract anywhere from around the equator posteriorly to the ciliary body anteriorly. We have therefore used the term anterior uveal neurilemmoma in recognition of our uncertainty of its exact site of origin.

We also consider that the tumours in four of the cases[5],[9-11] listed as neurofibromas in the review of Shields *et al.*[1] would now be termed neurilemmomas. It appears, then, that the majority of uveal nerve

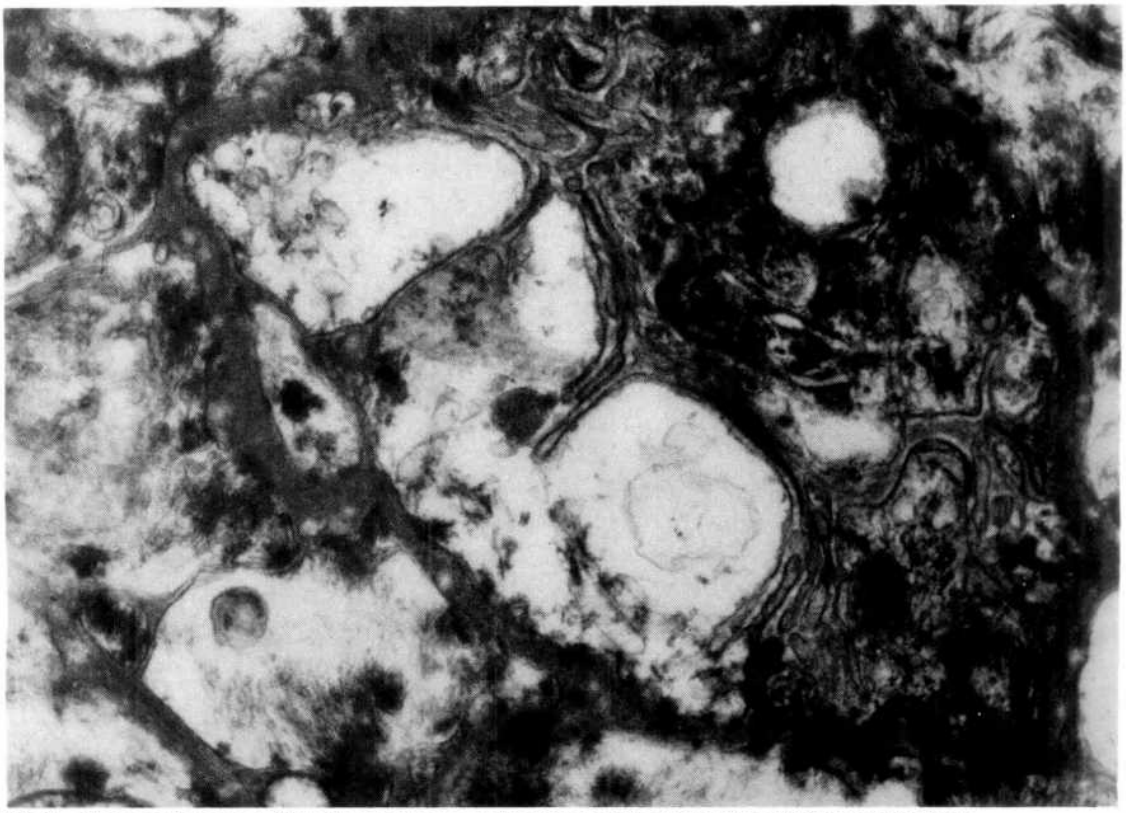

Fig. 8 *Electron micrograph. Cytoplasmic processes of the tumour cells entrap extracellular material to form pseudomesaxons. (×15 000).*

sheath neoplasms are neurilemmomas rather than neurofibromas.

The clinical features of this case illustrate some of the diagnostic problems of lesions presenting as ciliary body tumours.

On ophthalmoscopy the lesion appeared to be a cyst with a pigmented lining. This impression was supported by the highly translucent quality of the tumour and by its total lack of fluorescence on angiography. Ultrasonography was strongly suggestive of a solid lesion; computerised tomography was non-contributory; magnetic resonance imaging did not differentiate between a solid lesion and a cyst filled with highly proteinaceous fluid. In retrospect these apparent contradictions could be accounted for by the physical consistency of the neurilemmoma and its lack of pigmentation in the presence of an intact overlying pigment epithelium. The failure of magnetic resonance imaging to differentiate between a solid and a cystic lesion is presumably attributable to a high water content of the tumour.

It is worth emphasising that solid tumours, as well as cysts, may transilluminate if they are non-pigmented, as was reported with a similar case.[8] Further, the occurrence of a cystic appearance clinically does not necessarily indicate a benign lesion, as melanomas may occasionally be cystic.[12] Even melanin pigmentation, whether observed clinically or by light or electron microscopy, is not of absolute diagnostic value, since, as noted above, nerve sheath tumours may synthesise melanin. Heavy pigmentation of nerve sheath tumours is rare, however.

The lack of fluorescence by this tumour on angiography contrasts with the findings in previously reported cases.[1 2 13 14] This phenomenon was probably due to the fact that the overlying pigment epithelium was intact.

Episcleral 'sentinel' vessels are often present with ciliary body melanoma. Their presence in this patient, as in a previous case,[2] therefore, is not a reliable indicator of malignancy. Also it should be noted that the rate of growth of neurilemmomas, despite their benign behaviour, may surpass that of melanomas.[1] The ^{32}P test, an indicator of tumour growth rate, was not performed in this case. A previous report[1] suggests that a borderline result was likely.

Thorough assessment of the fellow eye as well as the rest of the patient is essential.[15] Cysts tend to be bilateral. The presence of extraocular malignancy or von Recklinghausen's disease may suggest the diagnosis, though a possible association between von Recklinghausen's disease and choroidal melanoma has also been recorded.[14]

In view of the clinical problem, fine needle aspiration biopsy might have yielded a definitive diagnosis; in general melanomas may readily be diagnosed by this method.[16] However, none of the several pathologists who saw the material was experienced in aspiration cytology of ocular lesions. Even had the diagnosis of neurilemmoma been made by aspiration cytology, the assessment of the malignant potential of nerve sheath tumours is usually based on mitotic counts rather than nuclear pleomorphism. This requires examination of histological sections. Thus the technique may have been of less value in this particular case.

Excision biopsy would seem to be the ideal way of reaching a definitive diagnosis, because, as well as providing suitable tissue for histology, it could itself be effective therapy, while preserving the eye. In this case, however, retention of a useful eye was considered unlikely, because excision of more than one-third of the ciliary body would have been required. Enucleation was therefore unavoidable, not only because (in the absence of a definite diagnosis) the tumour posed a possible threat to life, but also because it would inevitably have resulted in a blind, painful eye, whatever the diagnosis.

In conclusion, this case history is instructive because it demonstrates that the differential diagnosis of ciliary body tumours remains a difficult clinical problem, despite the availability of a wide range of modern diagnostic techniques. Excision biopsy, if technically feasible, may offer a reasonable alternative to enucleation in specialist centres.

The authors are grateful to Mr S S Johnston for bringing this case to our attention, to Mr J A W Ralston for expert technical assistance, to Drs N McMillan, D Hadley, and R J Hutchison for ultrasound, magnetic resonance imaging, and computerised tomography, respectively; also to Professor W R Lee for encouragement and advice.

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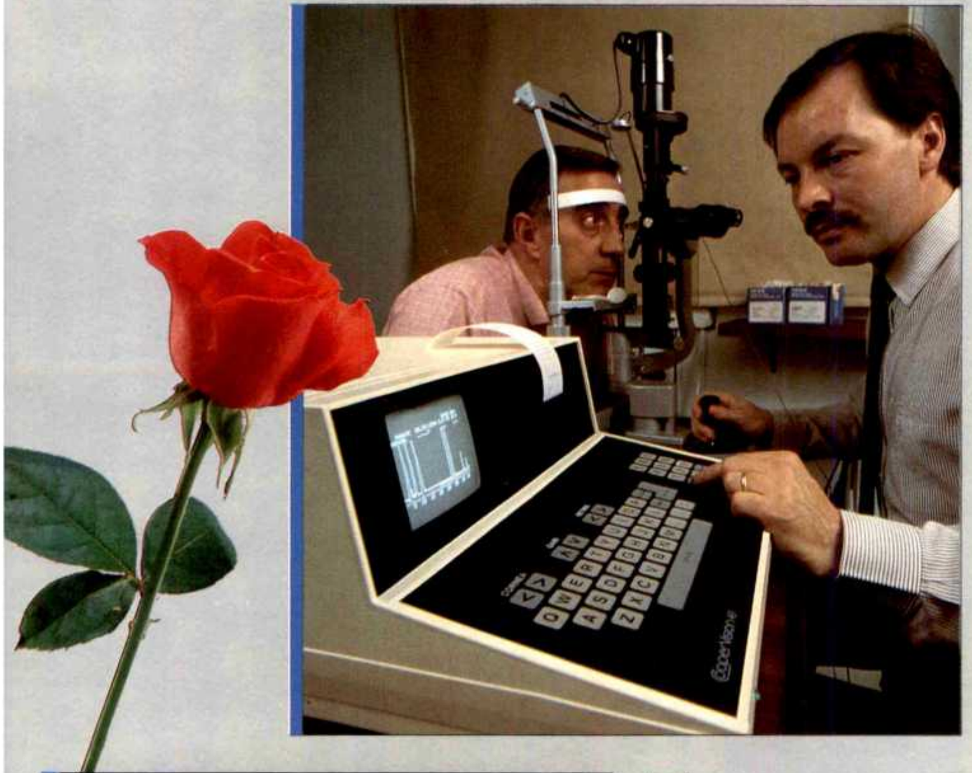

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Neurotropic malignant melanoma of right temple with orbital metastasis: a clinicopathological case report*

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SUMMARY A case is reported of neurotropic melanoma developed from a superficial spreading melanoma with minimal cytological deviation, situated in the right temple. The nine-year course was clinically characterised by local recurrences, involvement of the orbit and the parotid region via neurogenic invasion, and systemic metastases to lung, seventh rib, and the brain. The histopathology was characterised by fascicles of dysplastic spindle cells, neuroid arrangement in loose fibrillary matrix, and peri- and intraneural permeation of the nerve trunks. Despite minimal atypism the neoplasm metastasised and had a fatal outcome. The spindle cell component of the neurotropic melanoma lacked melanogenesis; Fontana stains were negative. As previously demonstrated, the histogenesis of the neurotropic melanoma is possibly a Schwann cell differentiation of the dysplastic atypical melanocytes, as shown by the positive reactions to Bodian's stain.

Neurotropic melanoma, a rare type of spindle cell malignant melanoma, is considered a variant of desmoplastic melanoma.[1 2] Sutula *et al.*[3] reported a case of desmoplastic melanoma of the upper eyelid in 1982. Reed and Leonard[4] in 1979 reported 22 cases of neurotropic melanomas. Since then many other cases have been described.[5-7] Our patient is one of the rare cases in which ocular tissue was involved during the nine-year course of a neurotropic malignant melanoma.

Case report

In May 1976 a 46-year-old man noticed that a long-standing freckle in the skin of the right temple had lately started to grow larger, and on occasions it bled when scratched. The pigmented lesion was biopsied and then totally excised by a plastic surgeon. The pathological diagnosis was 'melanose de Dubreuil'. Three years later, in November 1979, a deep small nodule appeared in the scar of the previous surgery. This was excised and found to be a 'recurrent malignant melanoma', which was incompletely excised. In January 1980 a fourth procedure was performed by a neurosurgeon, in which a wider field of excision was performed and part of the bony lateral orbital wall was removed, when specimens were taken from the orbital tissue. The pathological report was 'metastatic extension of melanoma into the right orbit'.

At this point an ophthalmologist was consulted. The vision was 20/20 OU and the eye examination was unremarkable except for a slight limitation of mobility of the right eye on lateral and supralateral gaze and minimal ptosis and right frontalis muscle drop (eyebrow and eyelid) secondary to previous operations.

Extensive investigations revealed the absence of systemic metastases, and after numerous consultations a radical orbitectomy was performed followed by a local radiotherapy. The pathological examination showed intraneural malignant melanoma in the nerves situated in the fat of the lateral part of the orbit and in the area of the lacrimal gland. The orbital apex was free of tumour.

In July 1982 the patient suffered from severe right sided neuralgia, erythema, induration in the right parotid region, and right Bell's palsy. A biopsy from

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*This study was presented in part at the annual meeting of the Eastern Ophthalmic Pathology Society, St Thomas, 1 November 1985.

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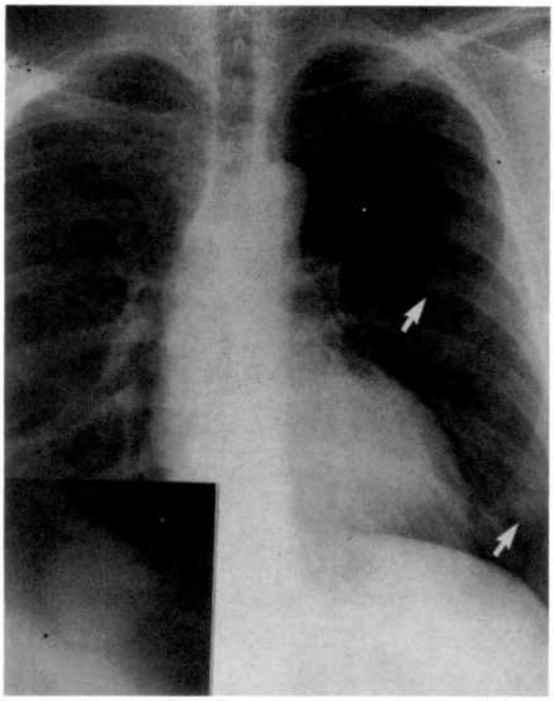

Fig. 1 *October 1982. Chest x-ray, two metastatic nodules in left lung (arrows).* Inset: *Tomogram of the nodule in the base of the lung.*

the parotid mass revealed a recurrence of the malignant melanoma along the ramifications of the facial nerve. Meanwhile, two metastatic nodules were seen in the chest x-ray (Fig. 1). A needle biopsy of one of the nodules proved it to be malignant melanoma metastasis. He was treated with irradiation to the parotid region, and chemotherapy was added after discovery of the lung metastases. Other possible metastases were detected by CT scans, in the seventh rib and in the right frontoparietal area of the brain (Fig. 2).

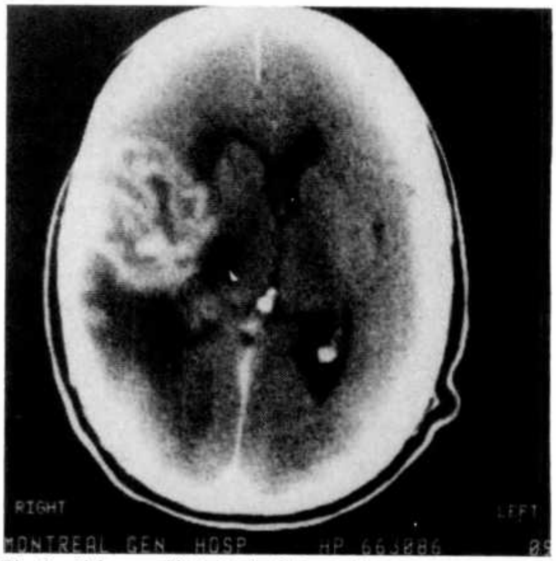

Fig. 2 *February 1984. Brain CT scan, large necrotic mass in the parietofrontal region, considered to be metastasis.*

The patient's condition deteriorated progressively, and he died in early 1985 at the age of 55. No necropsy was performed.

HISTOPATHOLOGY

I. The primary skin lesion, biopsied and excised in 1976, was found to be a superficial spreading malig-

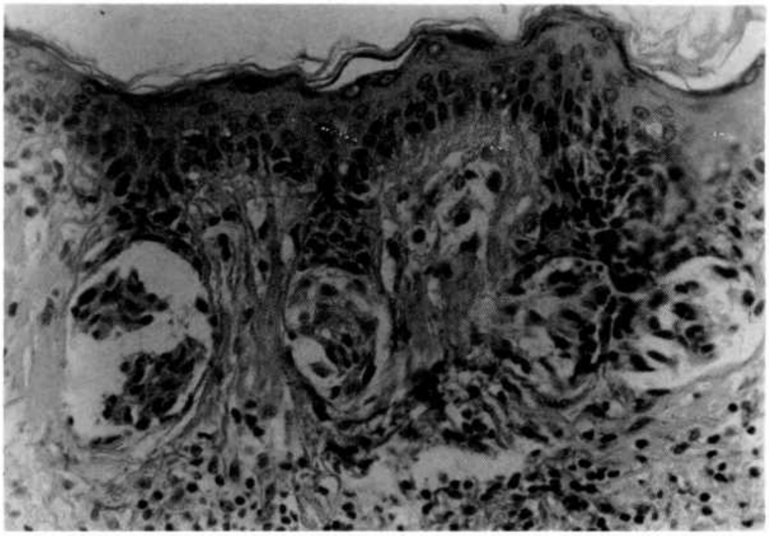

Fig. 3 *Histopathology of the precursory cutaneous melanotic lesion (1976), showing the features of superficial spreading melanoma. Atypical melanocytes were arranged as basilar nests in the elongated rete pegs. The cells were mostly spindled, a few naevoid and ballooned. (H and E).*

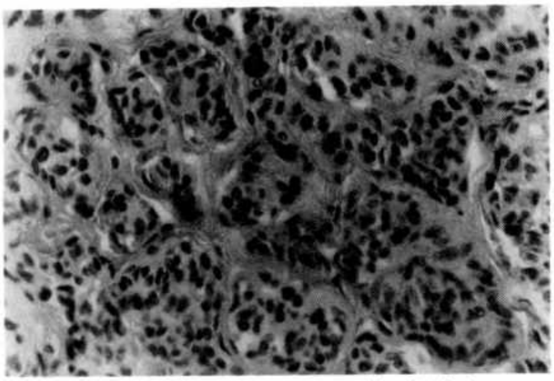

Fig. 4 *A section from the central part of the skin lesion: aggregation of atypical melanocytes giving the overall configuration of a naevus; the cells were spindle shaped and naevoid in type with minimal atypia. (H and E).*

nant melanoma with 'minimal cytological deviation' and had the following features (Fig. 3). The pattern of proliferating atypical melanocytes was variable—basal nests, intraepithelial nests, and pagetoid and in-situ-like patterns. The cell types of the atypical melanocytes were pleomorphic, small and large round, a few epithelioid, ballooned, and mainly spindled. The atypia was classified as mild, the divergence in nuclear size was minimal; some nuclei showed prominent nucleoli, and there was no mitosis. The subepithelial tissue (or dermis) showed patchy mononuclear cell infiltration. The tumour cells extended deep in the dermis to the level of the sweat glands (1·4 mm in depth) and permeated the perineurium of the peripheral nerves at the deep edge of the dermis. In the centre of the lesion there was a nodule composed of aggregations of plump spindle cells which had the overall configuration consistent with a naevus, though more detailed study pointed to a 'minimal deviation melanoma' (Fig. 4).

II. The recurrent skin lesion which was incompletely removed in November 1979 and then underwent a wider excision in January 1980 showed the picture of 'a recurrent cutaneous malignant melanoma with intraneural invasion of the nerves'. In the superficial part of the mass the melanoma cells were pleomorphic (Fig. 5a)—naevoid, with a few epithelioid and multinucleated cells; the predominant cells were elongated plump spindle cells arranged in fascicles. The Fontana stain was weakly positive. The deeper portion of this lesion was composed of elongated slender spindle cells (Fig. 5b) with a neuroid arrangement in a background of loose fibrillary matrix. Some of the cells were aligned end to end. The cytoplasm of the cells was pale. The nuclei were oval and had densely uniform chromatin. Some nuclei showed margination of the chromatin and prominent nucleoli, indicating some degree of atypism, but mitotic figures were not evident. When the cells were cut horizontally, they appeared as small spindle cells. Intraneural invasion of many nerves with the same type of cells was seen. This portion of the tumour was negative for Fontana stain, but Bodian stain showed rigid silver-positive fibrils (axons) to be present.

III. The orbital biopsy obtained during the operative procedure of January 1980 showed amelanotic elongated spindle cells permeating the nerve trunks in the area of the lacrimal gland (Fig. 6). The cells had

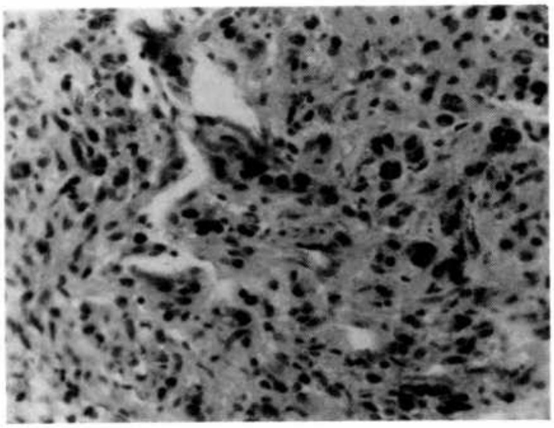

Fig. 5a

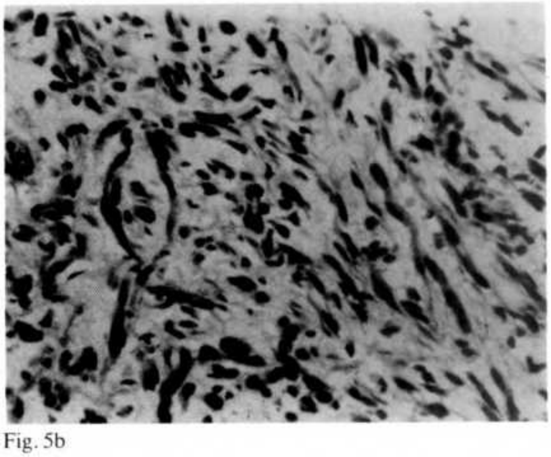

Fig. 5b

Fig. 5 *Recurrent malignant melanoma of the skin (November 1979).* (a) *The cells were pleomorphic, spindle shaped, epithelioid, and multinucleated, and some showed mitotic figures.* (b) *Deep portion of the melanoma showing slender spindle cells arranged in fascicles in a loose fibrous matrix. The cells were aligned end to end. Their nuclei were elongated, hyperchromatic, different in size, and mitosis was not a prominent feature. (H and E).*

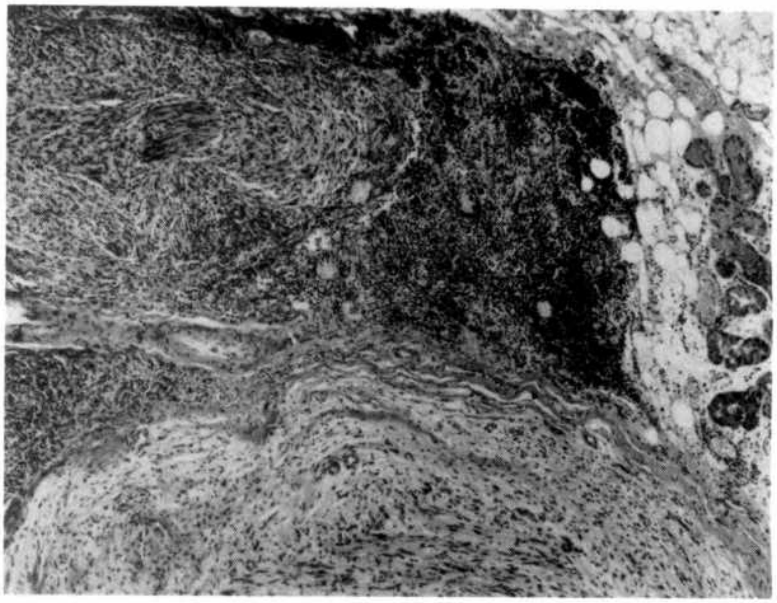

Fig. 6 *Orbital biopsy (January 1980). Lacrimal acini (on the right), the involvement of two nerves with tumour cells.* Above: *the normal trunk was surrounded by the tumour cells.* Below: *the tumour cells totally invaded and expanded the nerve. (H and E).*

histopathological characteristics like those seen in the deep part of the skin lesion. The pathological diagnosis was 'orbital metastasis of a neurotropic malignant melanoma by peri- and intraneural extension'.

IV. In the specimen of the radical orbitectomy of April 1980 residual metastatic neurotropic malignant melanoma involved numerous orbital nerves in the area of the lacrimal gland in the lateral part of the orbit; the orbital apex was free of tumour. The histopathology was similar to that in the previous orbital biopsy, and the nerves were expanded with the same type of melanoma spindle cells. A mononuclear inflammatory cell reaction surrounded the involved nerves. Bodian's stain and S-100 protein immunoreactivity were positive.

V. The biopsy, which was obtained from the parotid region in July 1982, showed a neuroid arrangement of the same type of spindle cells. The melanoma cells were found to be intraneural and in the soft tissue outside the nerve sheaths. Fontana stains were negative, while Bodian's stain and S-100 protein immunoreactivity were positive. The diagnosis was 'metastatic extension of a neurotropic malignant melanoma along the ramifications of the facial nerve'.

The final clinicopathological diagnosis was: (1) neurotropic malignant melanoma arising on top of a superficial spreading melanoma with 'minimal cytological deviation'; (2) multiple metastases through neurogenic routes to the orbit and the parotid region; (3) systemic metastases to the lung, seventh rib, and possibly to the brain.

Discussion

Neurotropic melanoma, as recently described by Reed and Leonard,[4] is a rare type of spindle cell malignant melanoma that invades the dermis from one of the following precursory epidermal lesions: (1) lentiginous melanoma, either a lentigo maligna or acral lentiginous melanoma; (2) a minimal deviation melanoma,[8 9] that is, a boderline lesion in which the histopathology mimics that of a benign naevus; (3) a de novo variety which lacks the evidence of a previous melanotic epidermal lesion.

The precursory lesion in our patient had the characteristic features of superficial spreading melanoma in its radial growth component, while its vertical growth phase was consistent with a minimal deviation melanoma. Dabbs and Bolen described a case of superficial spreading melanoma in which neurosarcomatous features were evident in the metastases.[10]

Most neurotropic melanomas occur on the exposed surfaces of the head and neck. In Reed and Leonard's series[4] they developed primarily on the temple in three out of 22 patients. The orbit was not involved in any of the three cases, but two of them died with involvement of the central nervous system.

The histopathology of neurotropic melanoma has distinctive features. The pattern is characterised by, first, fasciculation: the dysplastic spindle cells of the epidermis invade the dermis in the form of fascicles of elongated slender spindle cells; and, secondly, neurotropism: the spindle cells have the affinity to permeate the peripheral nerves, and invasion of adjacent structures occurs via perineural and intraneural extensions.

A neuroid pattern tends to occur in soft tissues outside the nerve sheaths and in uncontrolled recurrent lesions. The picture appears as masses of spindle cells with neuroid arrangement. The neurotropic melanoma may be associated with a desmoplastic component, which leads to the production of bulky subcutaneous tumefactions.

As to cell type, these tumours are composed of slender, elongated, spindle cells usually aligned end to end. The cytoplasm is pale and the nuclei are oval and have dense chromatin. Some nuclei show margination of the chromatin and prominent nuclei. They lie in a background of loose fibrillary matrix rich in reticulin. In transverse sections cells appear as small spindle types.

In general the tumour cells show minimal atypism, but some nuclei are of different size and shape and contain prominent nuclei. Mitosis is scarce.

Despite the minimal features of atypism the behaviour of these tumours is aggressive and characterised by multiple recurrences, distant metastases, and fatal outcome. The neurogenic extension of the tumour cells poses great difficulty in effecting a complete local excision of these lesions and so total cure. In our patient a radical orbitectomy and wide excision of adjacent structures were performed, yet a neurogenic extension along the branches of the facial nerve resulted in a recurrent metastasis in the parotid region two years after surgery.

The orbital invasion from the primary skin lesion in the temple occurred by neurogenic spread either along nerve fibres connecting the first and second branches of the trigeminal nerve (V-I and V-II) though small canals in the lateral bony orbital wall or around the orbital rim following the branches of the lacrimal nerve.

Schwann cell differentiation has been suggested in the histogenesis of neurotropic melanomas.[5 11] This was supported by certain observations made in light and electron microscopic studies of these tumours. The spindle cells are difficult to differentiate from Schwann cells and fibroblasts; they demonstrate marked affinity for cutaneous peripheral nerves and tend to occur in neuroid arrangements. Absence of melanogenesis: the spindle cells were amelanotic and Fontana stain was negative. In electron microscopic (EM) studies[5 10] melanosomes were absent. But Schwann cell features were identified on EM studies.[10] Argyrophilic fibres that have the characteristic of axons were demonstrated in most cases with Bodian's stain.

The S-100 protein immunoreactivity test, although not specific for Schwann cells, is useful in differentiating desmoplastic and neurotropic malignant melanomas from other types of spindle cell tumour which cause diagnostic confusion (leiomyomas, spindle cell variant of squamous cell carcinoma, tumours of fibreoblastic origin, atypical fibroxanthoma, and adaptive fibroplasia). The only spindle cell tumours which stain positively with S-100 protein are neural tumours and spindle cell malignant melanomas.[12] In our case the spindle cells in the deep part of the cutaneous recurrence of the malignant melanomas, the orbital extension, and the metastasis in the parotid region all stained with S-100 protein and were all amelanotic. Warner *et al.*[11] presented three cases of neurotropic malignant melanomas in which the spindle cells stained with S-100 protein and melanosomes were absent on EM studies. S-100 protein-positive staining of the spindle cells in neurotropic malignant melanoma with the absence of melanogenesis is suggestive of the Schwannian nature of these cells. It is generally accepted that Schwann cells and melanocytes are derived from related precursors as neural crest derivatives. Schwann cells may become facultative melanocytes, and melanoblasts may assume Schwannian characteristics. Abundant morphological evidence illustrates the overlapping spectrum of differentiation among melanocytic and Schwannian lines. Such cases include the melanocytic schwannoma, pigmented neurofibroma, desmoplasmic malignant melanomas, and common cutaneous naevi.

Why there is a sudden transition from a melanocytic component to fascicles of Schwannian-spindle cells is still unclear. Many theories have been suggested. Cramer[13] proposed the possibility that these tumour cells originate from the nerve-sheath precursor stage of the melanocytic differentiation pathway. The recurrences may reflect the persistence of neoplastic stem cells in the proximal nerve sheath. Reed and coworkers[4] suggested that dermal melanocytes in contact with neurites transform into Schwann cells, melanogenesis is reduced, and fibrogenesis appears. Warner[14] stated that the phenomenon of phenotypic mixing or conversion in neurotropic melanomas could be explained by cell hybridisation between dysplastic melanocytes and Schwann cells with variable expression.

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Infiltrating orbital granular cell tumour: a case report and literature review

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SUMMARY A surgical biopsy of an infiltrative retrobulbar mass in a 44-year-old man was diagnosed as granular cell tumour. Electron microscopy and immunoperoxidase stains were used to confirm the diagnosis and to study the histogenesis of this rare soft tissue neoplasm. S-100 stain was positive, while neuron-specific enolase and myoglobin stains were negative, suggesting a non-specific neural origin for the cells. The capability of this tumour to invade surrounding tissues has seldom been described in the orbit and is demonstrated by this case.

Granular cell tumour is an unusual neoplasm with uncertain histogenesis that rarely occurs in the orbit. It is regarded as a benign lesion, though it may locally invade surrounding tissues. The following case exemplifies such infiltrative behaviour within the orbit.

Case report

CLINICAL FINDINGS

A male native Indian boiler maker was first seen in Alberta in December 1984 at age 44 complaining of progressive horizontal diplopia of one month's duration. His corrected vision was 20/60 right and 20/20 left and he had restricted right abduction and supraduction. A CT scan showed an irregular enhancing mass posterior to the right globe and inferotemporal to the optic nerve. A biopsy of this lesion was reported as atrophic skeletal muscle with marked fibrosis and low grade chronic inflammation. With a presumed diagnosis of fibrosing pseudotumour, he was started on a course of oral prednisone.

Over the next 10 months his vision and diplopia subjectively worsened and he was referred to Vancouver in October 1985 for further evaluation. He had no other ocular or systemic complaints and was on no medications. Past medical history included three years of diet controlled diabetes mellitus and pulmonary tuberculosis in 1961. The family history contributed nothing relevant.

On physical examination his visual acuity remained at 20/60 OD and 20/20 OS, and visual fields were full to confrontation. The interpalpebral fissures were 9 mm right and 8 mm left. The right globe was elevated 2 mm and laterally displaced 1 mm. Exophthalmometry measured 15 mm right and 12 mm left. Ocular movements were full on the left but on the right were restricted to 10° in abduction and elevation with normal remaining ductions. Applanation tonometry was 14 mm bilaterally. Pupils were equally reactive to light and accommodation. Fundus examination showed choroidal folds inferolateral to the macula on the right side.

Routine blood analysis and chest *x*-ray were normal. A CT scan showed a uniformly enhancing homogeneous soft tissue mass, 13 by 13 by 15 mm, in the right retrobulbar space with well defined posterolateral margins but irregular medial border (Fig. 1). It indented the globe posteriorly and displaced the optic nerve medially (Fig. 2). No calcification was seen. Ultrasound indicated slight thickening of the sclera adjacent to the mass.

Visually evoked potentials were delayed and of low voltage for the right eye, with a broad peak with multiple small components, suggesting optic neuropathy secondary to an infiltrative rather than a compressive process.

On 11 October 1985 the patient underwent lateral orbitotomy under general anaesthesia. A firm, rounded, tan-grey mass was noted posterior to the globe and spreading inferolaterally next to the lateral rectus muscle. The tumour was sclerotic, with little vascularity, and appeared to invade the sclera and

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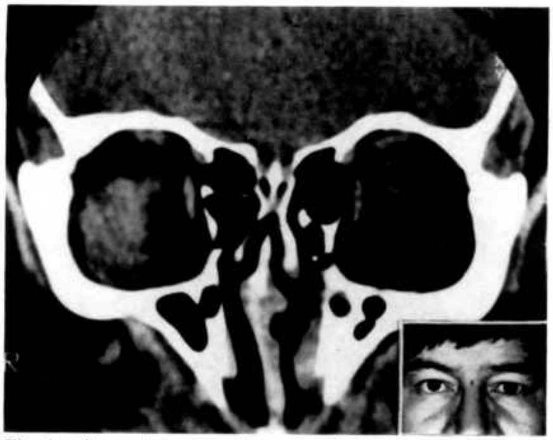

Fig. 1 *Coronal computed tomographic scan shows an irregular mass in the right inferolateral orbit in contact with the optic nerve. Inset shows patient with right proptosis and inferior scleral show.*

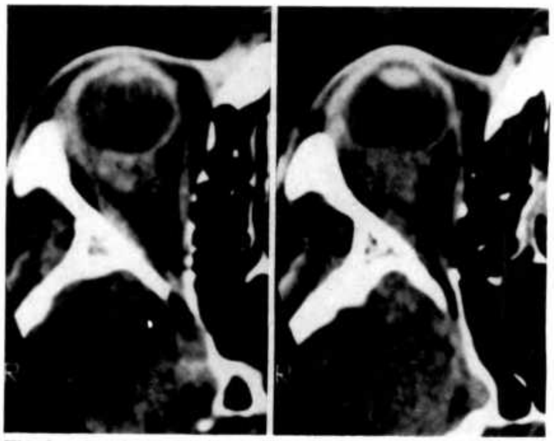

Fig. 2 *Axial computed tomographic scan shows right retrobulbar irregular mass displacing the optic nerve medially and indenting the globe posteriorly.* Left: *superior cut.* Right: *inferior cut.*

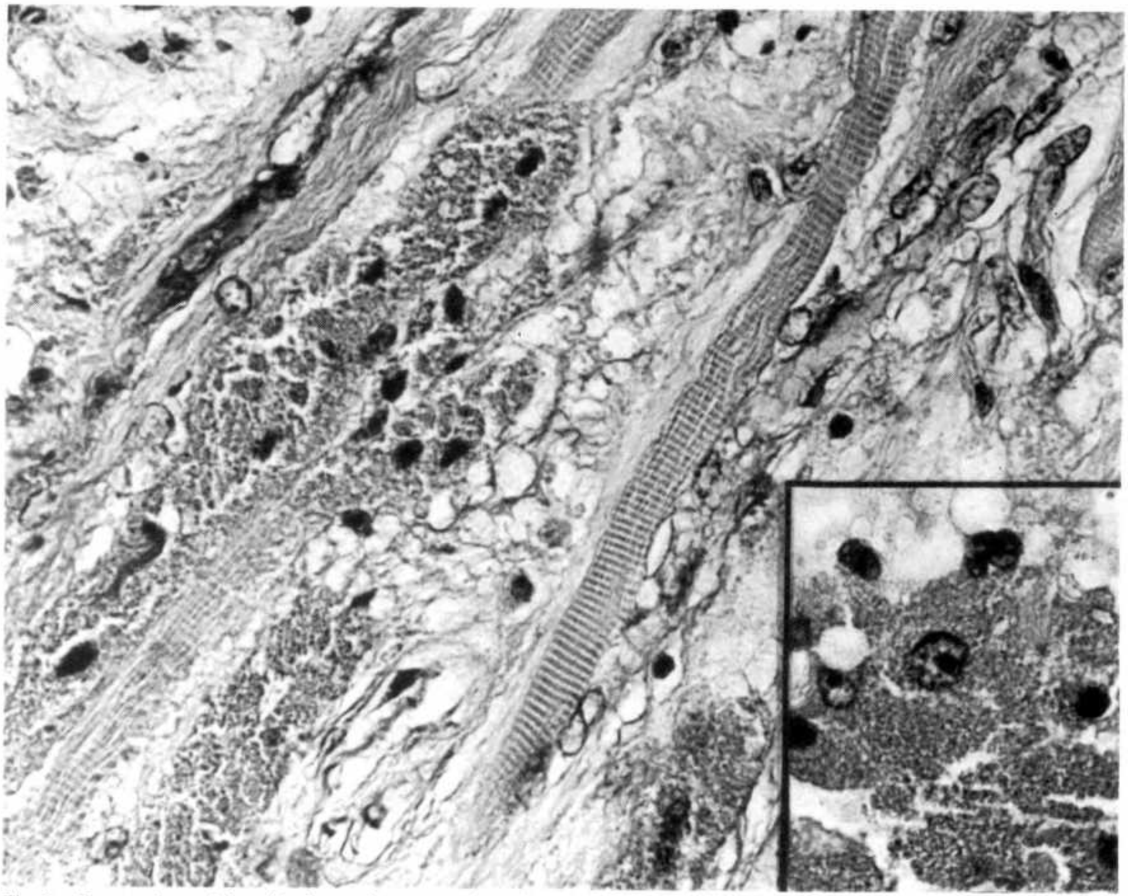

Fig. 3 *Tumour from right orbit shows plump granular cells invading surrounding striated muscle cells. Inset shows individual cells with prominent nucleoli and cytoplasmic granules. (Haematoxylin and eosin).*

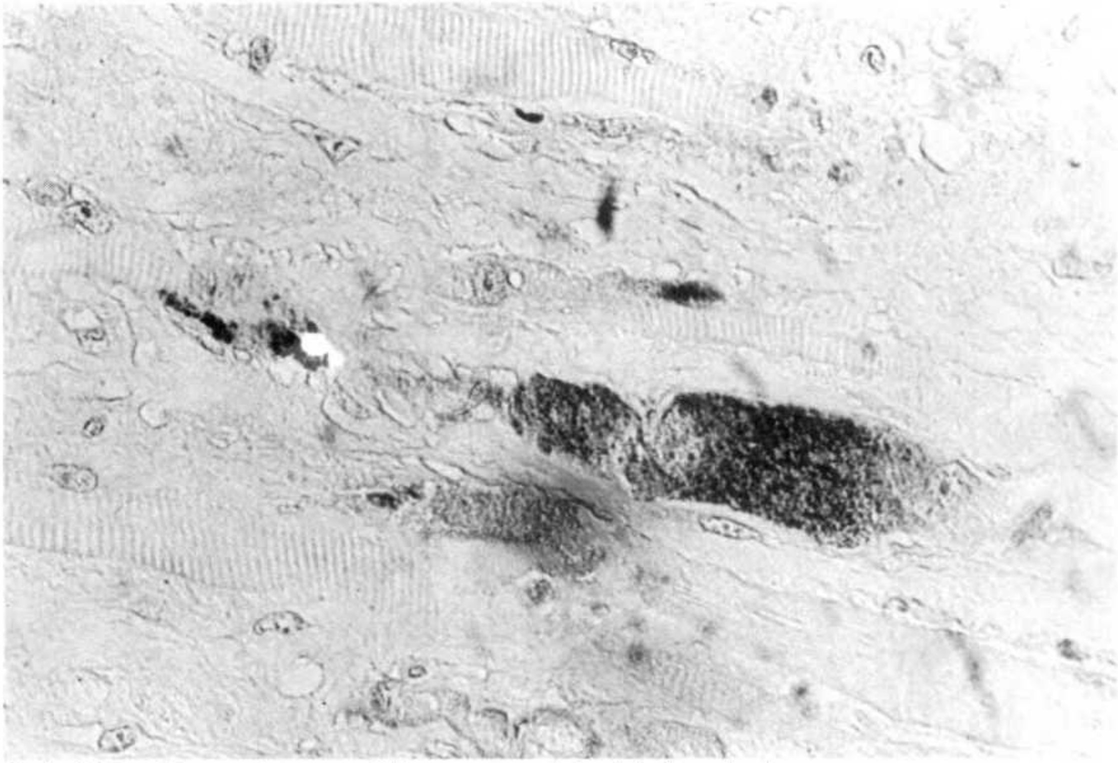

Fig. 4 *S-100 positive granular tumour cell lies among non-staining skeletal muscle cells.*

around the optic nerve, making complete excision impossible. Multiple sections aggregating to 1 cm were removed for pathological study and either fresh frozen or fixed in formalin, glutaraldehyde, and B_5.

PATHOLOGICAL FINDINGS

The tumour consisted of nests and ribbons of large round and polygonal cells. These contained paracentral, vesicular nuclei with prominent nucleoli and abundant cytoplasm replete with striking coarse eosinophilic granules (Fig. 3). The cells lay close to peripheral nerve bundles and normal striated muscles and were surrounded by dense fibrous scar tissue with a few scattered lymphocytes and plasmacytes. Neither mitotic figures nor necrosis were present.

The cytoplasmic granules were moderately periodic acid Schiff positive, diastase resistant, and stained Indian red with Masson's trichrome. They were negative for luxol fast blue. Bodian stain showed individual axons streaming alongside many of the granular cells. The tumour cells were strongly positive for S-100 protein (as were the Schwann cells in nerve bundles but not skeletal muscle fibres) and negative for myoglobin and neuron-specific enolase (Fig. 4).

Characteristic ultrastructural features were noted on electron microscopy.[1] The granular cells lay mostly in small clusters and had short interdigitating processes with rare primitive intercellular junctions (Fig. 5). A basement lamina often surrounded clumps but did not extend between adjacent individual cells. The nuclei were irregularly oval or round, with dispersed chromatin and medium sized nucleoli. The cytoplasm bulged with numerous pleomorphic lysosomal-like round bodies lined by single and occasionally double limiting membranes and filled with granular dense material, numerous small vesicles, and concentric laminated bodies (Figs. 6, 7). The cytoplasm also contained free ribosomes, sheets of mitochondria, irregularly arranged intermediate filaments (Fig. 8), and one membrane bound space containing a group of collagen fibres. A second more sparse population of single small angulate cells contained oblong bodies composed of fibrillary material surrounded by a unit membrane (Fig. 9). Small nerves and striated muscle fibres were also present but were distinctly separate from the tumour cells.

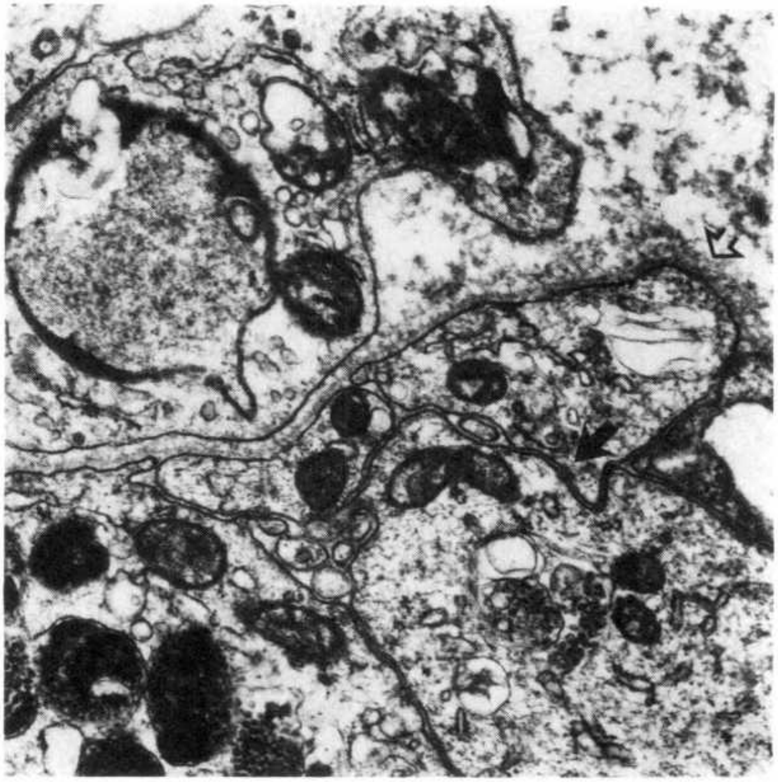

Fig. 5 *Clusters of granular tumour cells are surrounded by a basal lamina (open arrow) and connect with interdigitating processes with primitive junctions (solid arrow).*

Discussion

CLINICAL FEATURES

Over 500 cases of granular cell tumours have been reported[2] since the first case in the tongue by Abrikossoff in 1926.[3] Almost any organ or body tissue may be affected, though the most common sites are tongue, chest wall, and arm. Other cases have occurred in larynx, digestive tract, breast, female anogenital region, and pituitary stalk.[4]

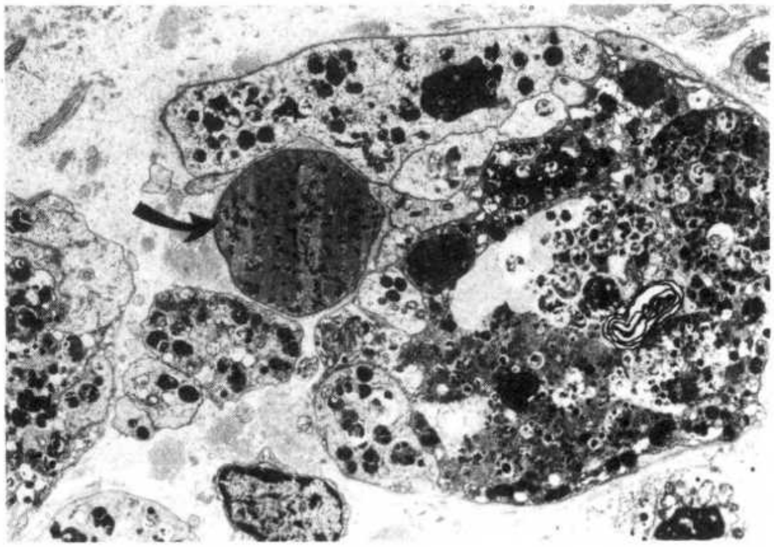

Fig. 6 *Several granular cells containing pleomorphic dense granules; complex vesicles and a myelin figure surround a muscle fibre (arrow).*

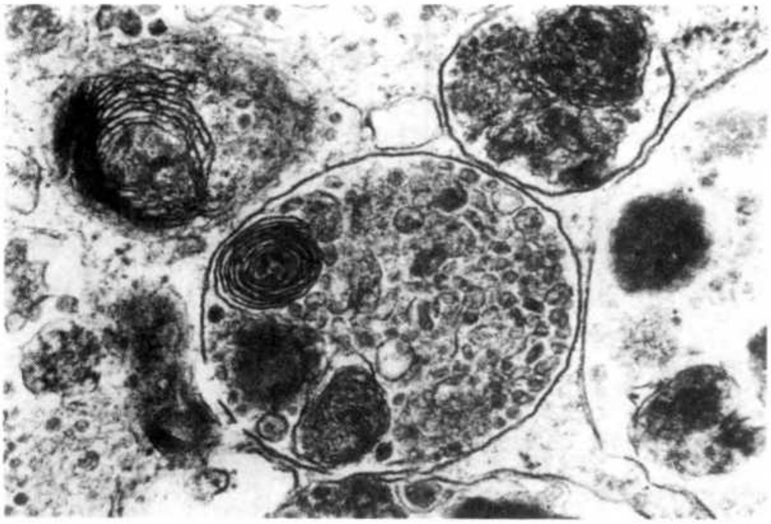

Fig. 7 *Complex cytoplasmic vesicles contain lamellar figures and smaller vesicles and granules.*

The tumour may occur at any age, though is most common between 40 and 70 years. Women are more frequently affected than men. It typically presents as a solitary, non-tender, firm nodule less than 6 cm in diameter present for less than a year. It may be well circumscribed or infiltrate into the surrounding tissue. Between 10 and 15% of granular cell tumours are multicentric and 1 to 3% are malignant.[5]

Orbital involvement has previously been described in only 15 patients.[6-19] Other cases in or near the eye have arisen in uvea, conjunctiva, caruncle, lacrimal sac, eyebrows, and eyelids.[18] Retrobulbar tumours adjacent to the optic nerve have been reported four times previously[11 12 15 18] and in one case caused optic neuropathy[12] similar to our case. Unlike their counterparts elsewhere in the body, granular cell tumours in the orbit have characteristically been described as discrete and well encapsulated. Only one case of orbital malignancy has been recorded.[6]

HISTOGENESIS

The histogenesis of granular cell tumour remains controversial. An origin from striated muscle was first proposed by Abrikossoff[3] and appeared to be supported by tissue culture studies of Murray.[20] However, development of tumour in areas lacking muscle and the lack of typical muscle ultrastructural components have largely discounted this theory.

Azzopardi suggested that these tumours were of histiocytic origin because of the abundance of

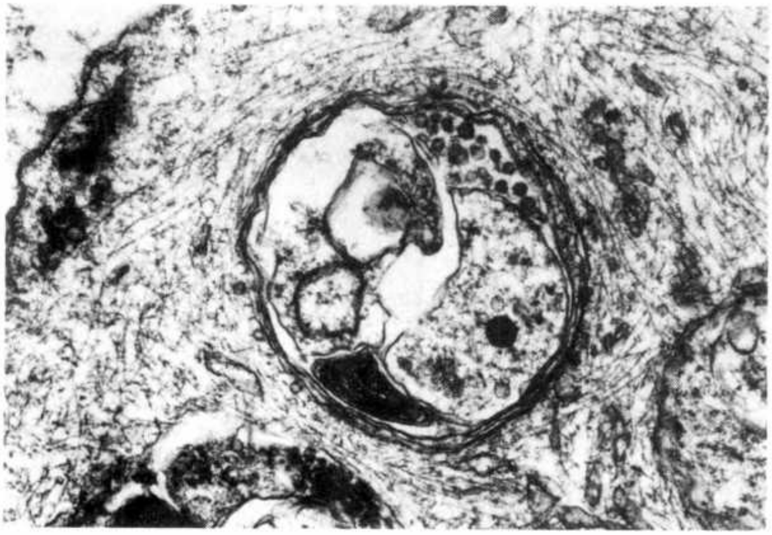

Fig. 8 *Several complex vesicles nest in a bed of intracytoplasmic filaments.*

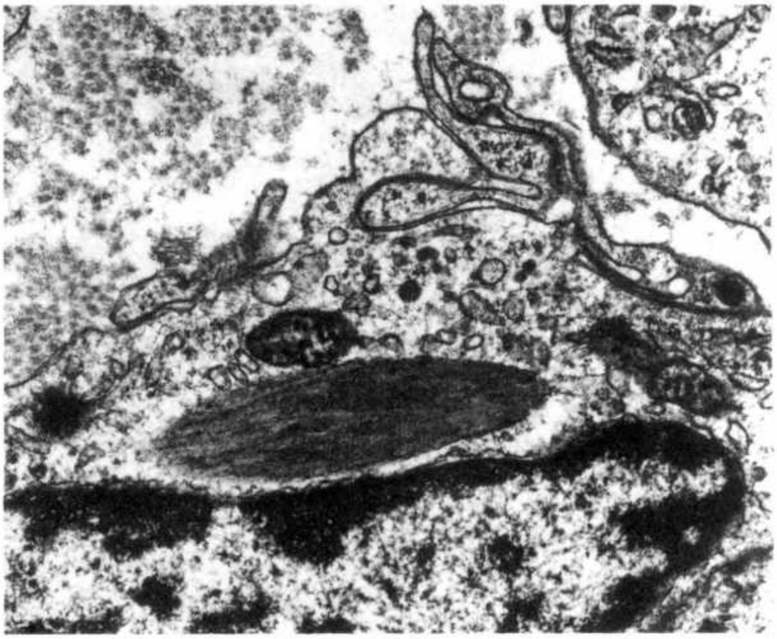

Fig. 9 *Filamentous angulate body lies adjacent to granular cell tumour nucleus.*

lysosomes and their enzymes.[21] This is now considered unlikely, because the tumour cells lack specific histiocytic markers such as lysozyme and α_1 antitrypsin.[22]

In 1935 Feyrter suggested a neural origin, and this is currently receiving increasing support.[23] Candidates for the cell of origin include perineural fibroblasts,[24] Schwann cells,[25] and primitive precursor mesenchymal cells with the potential to differentiate into Schwann or granular cells.[22] Proponents of Schwann cells note the tumour's frequent association with peripheral nerves and electron microscopy showing a basal lamina around cells and cytoplasmic inclusions reminiscent of degenerated myelin. Others report positive histochemical staining of the granules for cerebrosides and other myelin degeneration products. However, we and others found only cell groups surrounded by a basal lamina rather than individual cells as in Schwann cell tumours.[22] Further, our case stained negative for lipid and myelin, confirming similar results of Morgan.[13]

Special immunochemical stains also support a neural origin. S-100 protein is an acidic protein present in glial cells of the central nervous system and peripherally in Schwann cells, spinal ganglion satellite cells, melanocytes, and other cells of neural crest origin. Granular cell tumours have been consistently S-100 positive in several series[26 27] but are negative for myoglobin, a muscle marker.[28] Our case showed a similar pattern. Neuron-specific enolase, present in nerve cells and absent in Schwann cells, was identified in eight granular cell tumours tested by Rode *et al.*,[29] but was negative in ours.

Thus the evidence, corroborated by our findings, suggests neural differentiation for granular cell tumour, but the exact cell of origin remains uncertain.

TREATMENT

The treatment of granular cell tumour is wide surgical excision. The reported local recurrence rate is less than 7%.[2] Radiotherapy has not proved helpful.[5]

In previous cases the orbital granular cell tumour, with two exceptions,[6 8] appeared to be well encapsulated and shelled out relatively easily at surgery. Our case demonstrates the potential for the tumour to infiltrate tissues in the orbit as it does elsewhere in the body. Progression and extension make total exenteration a grim probability.

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Diagnosis of orbital myositis by nuclear magnetic resonance imaging

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SUMMARY Two cases of orbital myositis are reported in which precise identification of the involved muscle was possible with the use of surface coil nuclear magnetic resonance (NMR) imaging. A clinical response to oral steroids in both cases coincided with a marked reduction in the abnormal thickening of the muscles as seen on the NMR images.

The diagnosis of orbital 'space occupying lesions' poses a considerable challenge to the clinical acumen of the treating surgeon. Over the years several techniques, both invasive and non-invasive, have been developed and employed to differentiate such lesions.[1] These have their own advantages and limitations and are often complementary to each other. The most recent innovation is nuclear magnetic resonance (NMR) imaging, and early impressions from clinical evidence indicate certain distinct advantages.[2,3]

NMR imaging of the ocular and orbital structures has been in use for four or five years.[2-6] In addition to being a non-invasive, non-ionising method for imaging soft tissue its chief advantage lies in its ability accurately to localise pathological lesions without artefactual interference from the bony tissue that surrounds the orbital structures on all four sides.[3,7] Apart from precise anatomical localisation, valuable information about the composition of tissues can also be obtained, in some situations, by studying the proton density (PD) and proton spin lattice relaxation time (T1) images.[2,3]

We report two cases of subacute orbital myositis in which precise localisation of the inflammatory process to the lateral rectus muscle was demonstrated by NMR imaging and a clinical response to oral steroids coincided with corresponding reduction in the muscle mass on the NMR images.

Patients and methods

The patients were examined in the Aberdeen NMR imager, developed and built in the department of Bio-Medical Physics and Bio-Engineering at the University of Aberdeen. The imager is based on a four-coil, air-cored resistive magnet of 0·08 tesla which gives a resultant resonant frequency of 3·4 MHz for hydrogen protons. Data for each section, which may be either sagittal, coronal, or axial, are collected in 256 s by the 'spin-warp' method. The pulse sequence employed consists of readout pulses every 1000 ms with alternate readout pulses preceded by inversion. The inversion is accomplished by adiabatic fast passage with a continuous delay of 200 ms. In other words, the pulse sequence consists of interleaved saturation recovery (S1) and inversion recovery (S2) pulses (TR=1000 ms, T1=200 ms). After acquisition the data may be displayed as proton density, inversion recovery, or calculated T1 images on a grey-scale visual display unit. T1 is calculated for each element from the formula: $T1=200/\ln(2\times S1(S1-S2))$.[3] The section thickness is 10 mm and sections are made at 5 mm increments, allowing for complete examinations of the orbit.

CASE 1

A 53-year-old male was admitted with an eight-day history of redness and swelling of the right eye. The lids were oedematous and the conjunctiva congested and chemosed, especially over the insertion of the lateral rectus muscle. The globe showed a relative proptosis of 3 mm with increased orbital resistance. The eye was deviated nasally by 10 prism dioptres, and abduction was considerably restricted, with diplopia on dextroversion. The eyeball was normal in all other respects. The *x*-rays of the orbits and results of haematological investigations, serum biochemistry, and thyroid function tests were all normal.

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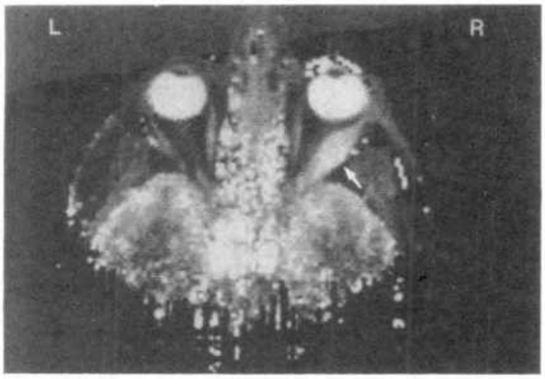

Fig. 1 *NMR image (calculated T1; long T1=white; short T1=black) of case 1 showing a fusiform enlargement of the right lateral rectus muscle (arrow).*

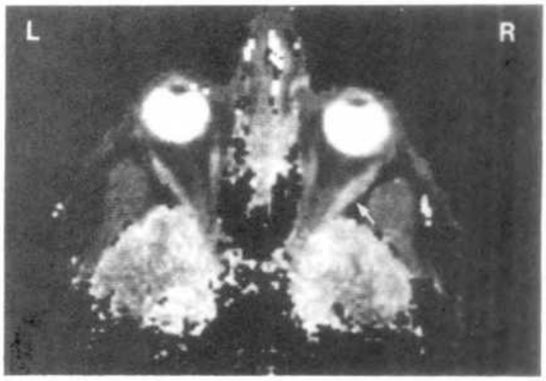

Fig. 3 *Calculated T1 image of case 1 performed 17 days after treatment with oral steroids. Note the considerable reduction in size of the right lateral rectus muscle (arrow).*

NMR scans of the orbit with a surface coil showed a gross fusiform enlargement of the right lateral rectus muscle (Fig. 1). A CT scan was also carried out. This showed the muscle to be enlarged, but the image was less well defined (Fig. 2). It failed to show the full extent of the muscle swelling. The patient was treated with 40 mg of prednisolone daily by mouth. Clinical improvement occurred rapidly, with recovery of the lateral rectus muscle function and decreased chemosis and congestion within a week. The steroid dose was gradually reduced to 20 mg per day. A follow-up NMR scan, 17 days after admission showed marked reduction in the thickness of the lateral rectus muscle (Fig. 3).

CASE 2

A 55-year-old female was referred with complaints of watering, redness, and swelling of the right eye of five days' duration. A history of eyelid/ocular contact with an insect some 24 hours previously was elicited, and she had been treated for angioneurotic oedema with topical steroids by her general practitioner. Ocular examination revealed lid oedema with considerable conjunctival chemosis and congestion. There was no proptosis and only a slight restriction of abduction of the right eye. The eyeball was normal in all other respects. *X*-rays of the orbit, haematological investigations, serum biochemistry, and thyroid function tests were normal. Surface coil NMR imaging of the orbits revealed a gross thickening of the right lateral rectus muscle (Fig. 4). A CT scan of the orbit also showed the muscle enlargement (Fig. 5), but, as in the first case, the latter method did not demonstrate the full extent of the muscle swelling. She was treated with 20 mg of oral prednisolone daily, and clinical improvement was observed within the first week. The eye could be fully abducted and the chemosis and congestion had subsided. She was discharged and the steroid dose reduced over the following weeks. A repeat NMR scan was performed

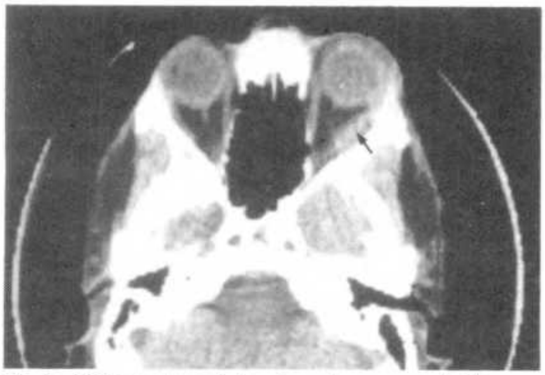

Fig. 2 *CT scan of case 1 showing enlargement of right lateral rectus muscle (arrow). The fusiform shape is not very obvious and the outlines are not clearly defined.*

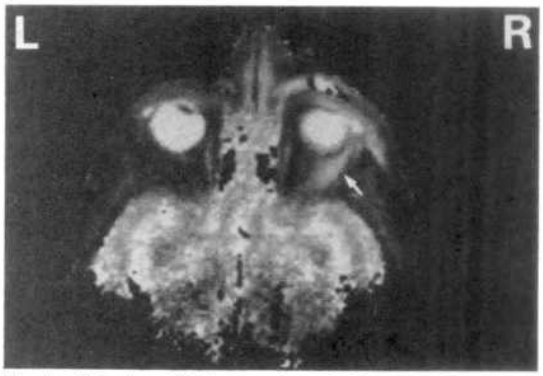

Fig. 4 *Calculated T1 image of case 2 showing a fusiform enlargement of the right lateral rectus muscle (arrow).*

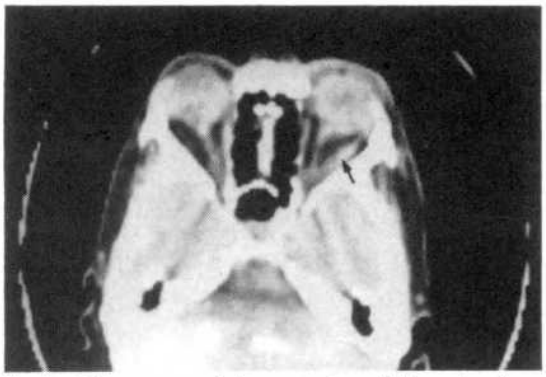

Fig. 5 *CT scan ase 2 demonstrating a thickened and enlarged right ' rectus muscle (arrow). Note that muscle enlargement app less by this technique.*

six weeks after admission and showed a complete resolution of the earlier lesion in the lateral rectus muscle (Fig. 6).

Discussion

Orbital fat, because of its relatively high hydrogen ion content, gives a very dark shadow on the T1 NMR image. This provides an excellent contrast for delineating outlines of other soft tissue structures such as muscle and nerve, both of which have a low hydrogen ion concentration and appear white or light grey. The extraocular muscles appear as thin strap-like structures running from the apex of the orbit to the wall of the globe, and the nerve forms a sinuous image within the cone formed by the muscles.[3,6] With the improved images produced by a surface coil other orbital structures such as branches of the trigeminal nerve and the ophthalmic vessels can be delineated.[6] The coats of the eye—sclera, choroid, and retina—appear as a homogeneous grey layer surrounding a dense white vitreous and the crystalline lens appears black. The bony orbital wall is not clearly visualised on the T1 image.[3]

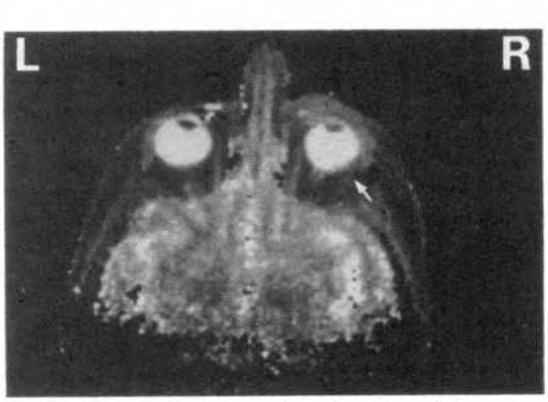

Fig. 6 *Calculated T1 image of case 2 performed six weeks after treatment with oral steroids. Note the complete resolution of the muscle swelling (arrow).*

Orbital myositis has been classified within the category of 'pseudotumours' of the orbit.[1,8] Its cardinal feature is a painful swelling usually of one ocular muscle. Other common conditions causing enlargement of extraocular muscles are Graves' disease, chronic inflammatory granulomas (pseudotumours), and neoplasms, either primary or secondary.[9] With the advent of ultrasonography, CT scanning, and now NMR imaging a precise diagnosis of myositis is possible, and it should be regarded as a distinct clinical entity.[9] The condition responds dramatically to systemic steroids, as illustrated by the above cases. It is important therefore to diagnose the condition with reasonable accuracy and attempt a trial of steroids before embarking on more invasive investigative and therapeutic measures.

In Graves' disease ocular muscle enlargement is uniform along the muscle length, and usually more than one muscle is involved. The degree of muscle involvement, however, is asymmetrical, some muscles being involved more than others. Increase in amount and anterior displacement of the orbital fat with forward bowing of the orbital septum are additional features.

In orbital myositis swelling may affect only a segment of the muscle, giving it a fusiform appearance, and usually only one muscle is involved.[9] This is demonstrated in both the cases presented (Figs. 1 and 4).

Differentiation of ocular muscle disorders from orbital neoplasia and pseudotumours is usually a simple task by NMR or CT scanning. Lymphoma, lymphosarcoma, and metastatic deposits usually present with a mass adjacent to or compressing the extraocular muscle or infiltrating its substance.[9] With metastatic carcinomas the tumour tissue appears as a discrete deposit with a longer T1 relaxation time than the adjacent muscle.[3] With pseudotumours the lesions appear as an irregular infiltration of the orbital tissues surrounding the muscle and are comparatively less well delineated.[3]

NMR and CT scans give sharp and well defined images, and permit better anatomical localisation than ultrasound. Being the least affected by bone images, NMR scanning gives the best definition of structures in the orbit,[3,6] but this makes it less suitable for detecting tumour infiltration into bone tissue. The margins of cortical bone are defined only where it interfaces with soft tissue and not with the air.[5] NMR also fails to demonstrate soft tissue calcification, for example in orbital granulomas, varices, and benign neoplasms. Small lesions of 1 or 2 mm diameter cannot be visualised by any of these techniques.[3] Multiplanar imaging is possible with NMR and CT scanning, but the increased radiation dose involved in multiplanar CT scanning is avoided in NMR imaging.[5] High doses of radiation may result from faulty collimation when a large number of fine sections are obtained for reformatting purposes. This is a definite advantage of NMR techniques. Prolonged or repeated NMR imaging has not shown any untoward effects.[10] This makes the technique very suitable for monitoring the progress of a lesion and its response to therapy. Since the T1 relaxation time and the proton density image of tissues vary according to their hydrogen atom content, valuable information on changes in composition of some tissues can now be obtained by NMR imaging. This was hitherto impossible except by biopsy.

The use of surface coils in NMR imaging has considerable potential in ocular and orbital diagnosis.[3 6] This will be realised as more clinical experience is gained with this technique and the technique itself is further refined. Improved spatial resolution of images by decreasing pixel size and section thickness is possible with magnets of high magnetic field strength. Study of substances other than hydrogen, such as sodium, potassium, and fluorine, may also be possible and may give further insight into tissue composition and probably increase the range over which tissue differentiation is possible.

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Spatial contrast sensitivity and the diagnosis of amblyopia

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SUMMARY The relationship was studied between spatial contrast sensitivity function and type of pathology of the visual system. Two characteristics were found to be typical for amblyopia: (1) there is a discrepancy between the high-frequency cut-off ('grating acuity') and the Snellen acuity; (2) the contrast sensitivity is strongly dependent on the width of the stimulus. In optic nerve degeneration a decrease in contrast sensitivity is found at low spatial frequencies. Decreased contrast sensitivity at high spatial frequencies is atypical but occurs in those disorders associated with decreased Snellen visual acuity. From these findings a relationship is defined which enables spatial contrast sensitivity tests to be used to differentiate between amblyopia and optic nerve degeneration.

The ophthalmologist is faced with the task of diagnosing the cause of any visual impediment. After optimal correction and examination by slit-lamp or ophthalmoscope there remain some patients in whom the diagnosis is not clear. Their visual loss may be due to optic nerve degeneration or to amblyopia ('lazy eye'). It would be helpful if a simple method were available to distinguish between these two possibilities. Determination of spatial contrast sensitivity function (CSF) might be such a relatively simple method.

The Snellen optotype chart is a measure of the minimum angle of resolution at high contrast. In CSF the maximum discernible spatial frequency can also be interpreted as a measure of the resolving power: the 'grating acuity' can be calculated from this frequency. Although the stimuli with which the visual acuity and the grating acuity are determined are quite different (optotypes and line patterns respectively), it is interesting to compare the visual acuity and the grating acuity because both values are measures of the spatial resolution at high contrast. The CSF provides more information than the Snellen acuity, while it also estimates the spatial resolution at low contrast or, in other words, how well coarser structures can be seen at low contrast.[1]

The study of contrast sensitivity function as it is related to several types of pathology is not new. Various workers have reported on contrast sensitivity in amblyopia[1-9] and in optic nerve disorders.[4 5] The CSF has been described in optic nerve lesions[10-12] and in cataract.[13] Most of these publications deal with rather small numbers of cases, and almost all concern our understanding of specific disorders of the visual system, but there are no reports on the evaluation of CSF as a diagnostic aid in neuro-ophthalmological practice.

The aim of this study was threefold: first, to determine to what extent the shape of the CSF is related to the particular type of pathology; secondly, to evaluate the effectiveness of spatial contrast sensitivity tests for the diagnosis of amblyopia, especially with regard to the differentiation between amblyopia and optic nerve degeneration with decreased visual acuity; and thirdly to compare the visual function in optic nerve degeneration combined with normal visual acuity with visual function in a group of normal eyes.

In a pilot study by Hagemans and Van der Wildt[9] in a small group of patients it was found that the

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dependence of contrast sensitivity on the width of the stimulus was much greater for amblyopes than for normal subjects or patients with other pathology.

Subjects and methods

The subjects who took part in this study were chosen from among the outpatients of an ophthalmological practice. They were divided into several groups according to the type of pathology, thus: amblyopia (n=98), optic nerve degeneration (n=42), and cataract (n=10). A group of normal persons (n=26), that is, without any known pathology or complaints, were also examined.

The group of patients with optic nerve degeneration comprised those who had suffered from optic neuritis in the previous three years, with or without other evidence of multiple sclerosis. Optic neuritis was electrophysiologically diagnosed in that period. This group was divided into two subgroups, those with normal visual acuities (greater than or equal to 1·0; n=16) and those with diminished visual acuities (less than 1·0; n=26). The group of cataractous eyes was examined to enable a comparison to be made between groups of eyes with decreased visual acuity originating from different causes.

Cases with evidence of multiple pathology were excluded. From a statistical point of view each patient was allowed to occur only once in the series. Hence in cases of binocular disease only one eye (chosen at random) was used. Five amblyopes had binocular disease, while 93 had monocular. The numbers of binocular and monocular cases of optic nerve degeneration were 7 and 35, and of cataract 4 and 6, respectively.

The mean age was 35 years, standard deviation 10 years, for both normal and amblyopic subjects; 45, SD 17, years for subjects in both optic nerve degeneration subgroups; and 59, SD 11, years for the subjects in the cataract group.

The visual acuity of all subjects was determined by the Snellen optotype chart.

DETERMINATION OF CONTRAST SENSITIVITY

The contrast sensitivity (CS) was determined by presenting vertical sinusoidal gratings on a television monitor. The contrast of the stimulus was variable; the contrast threshold was determined for each eye separately by a modified von Békésy tracking technique.[14] The spatial frequency of the grating and the width of the stimulus could be adjusted. The height of the stimulus always subtended 5° visual angle; the average luminance of the stimulus was 5 cd/m^2. The examinations were performed in a dark room. The grating was counterphased every 0·6 s to prevent after-images.

The CSF was determined for spatial frequencies ranging from 0·1 to 25·6 cycles per degree (c/deg) in steps of a factor 2. Up to 0·4 c/deg the viewing distance was 50 cm, resulting in a stimulus width of 32°; from 0·8 to 25·6 c/deg the viewing distance was 200 cm, which gave a width of 8°. For lower frequencies the stimulus had to be wider, because if there are fewer than 5 cycles within the stimulus the number of cycles has an influence on the CS.[15-18] The CS is defined as the reciprocal of the value of the contrast at the threshold.

When the CS was determined as a function of the width of the stimulus, the monitor was at a viewing distance of 100 cm; the width of the stimulus was changed from 16° to 1° in steps of a factor 0·5. The width dependence was determined at a spatial frequency of 1·6 c/deg.

The CS data were automatically plotted in double logarithmic form against spatial frequency or against the width of the stimulus, depending on the type of determination. The apparatus with which the measurements were performed was specially designed for clinical use.[19] The measuring procedure runs automatically and is controlled by a microprocessor system. The whole measuring sequence including patient instruction takes about 25 minutes for both eyes.

For each of the CSFs the corresponding grating acuity was calculated by extrapolating the high frequency part of the CSF to the maximum contrast (CS=1). A quadratic function was used for the extrapolation, as this type of curve yielded a good fit for the appropriate part of the CSF. The grating acuity is expressed as the reciprocal of the minimum angle of resolution in minutes of arc, as is the Snellen visual acuity. The acuity A (1/min of arc) is equivalent to a spatial frequency of 30×A [c/deg].

The slope of the CS between 1° and 4° width was taken as the measure for the width dependence of the CS. This was expressed as:

$$S=(\log(CS(4°))-\log(CS(1°))/\log(4).$$

Results

Point by point averaging of the data points of the CSFs within each of the groups yielded the group-specific CSFs. The curves for the group of normal eyes and for the group of amblyopic eyes are depicted in Fig. 1. The mean visual acuity for the group of normal eyes was 1·34; the mean grating acuity was 1·18.

As is to be expected from the lower mean visual acuity in the amblyopic eyes (0·39), contrast sensitivity at the higher spatial frequencies (CS(HF)) was low. This was associated with a decrease in the grating acuity, which had a mean value of 0·80.

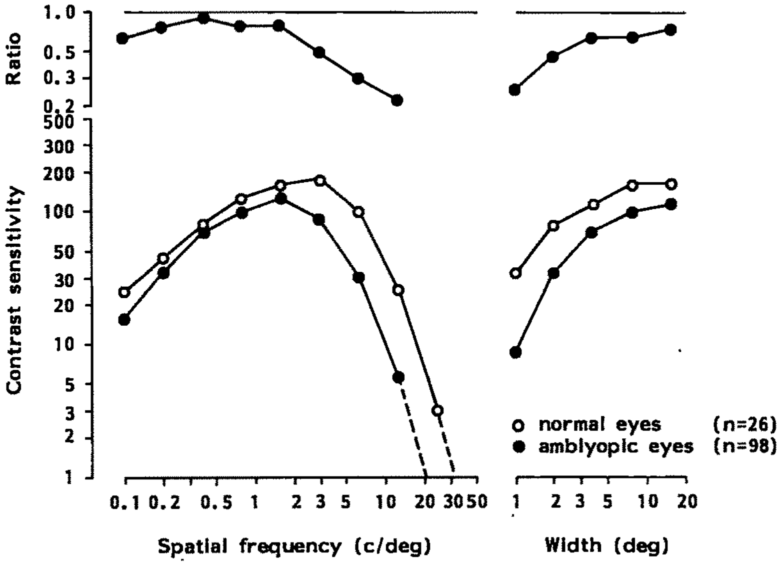

Fig. 1 Lower left: *Averaged CSFs for 26 normal visual systems and for 98 amblyopic eyes. The dashed lines at the high frequency end of the CSFs indicate extrapolation to the grating acuity.* Lower right: *The relationships between contrast sensitivity and width of the stimulus ('width dependence') for normal eyes and for amblyopic eyes.* Upper left *and* right: *Ratio of the two curves in the lower part with the normal one as the reference. The curve on the left (the ratio of the two CSFs) is called the 'visuogram'.*

Hence the resolving power calculated from the CSF was about twice the value determined with the Snellen letter chart. The graph at the top of Fig. 1 shows the ratio of the value for amblyopic eyes to that for normal eyes. This type of curve is called a 'visuogram.'[20] The difference between amblyopic and normal eyes became more pronounced at higher frequencies.

The right-hand graphs show the relationship between CS and the width of the stimulus. Below a width of 4° the CS decreased considerably, which means that for a narrower grating presentation more contrast is needed to reach the threshold. In the amblyopia group the CS decreased more rapidly as the width of the grating was reduced than in the normal group: the slope between 1° and 4° was much greater in the amblyopic visual systems. This result, which was anticipated in the pilot study performed by Hagemans and van der Wildt,[9] was confirmed by this study of 98 amblyopic eyes. The results were almost identical among subdivisions of the group of amblyopic eyes: 41 cases of anisometropia, 32 cases of strabismus, and 25 cases of unknown origin. These results are not shown here.

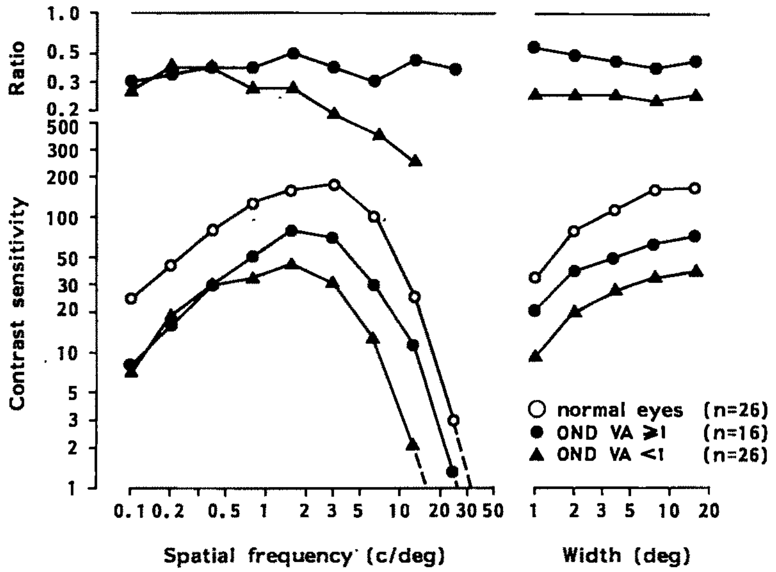

Fig. 2. Lower left: *Averaged CSFs for 26 normal eyes, for optic nerve degeneration with normal visual acuity (n=16), and with decreased visual acuity (n=26).* Lower right: *Width dependence for the same groups.* Upper: *Ratio curves with the normal curve as the reference.*

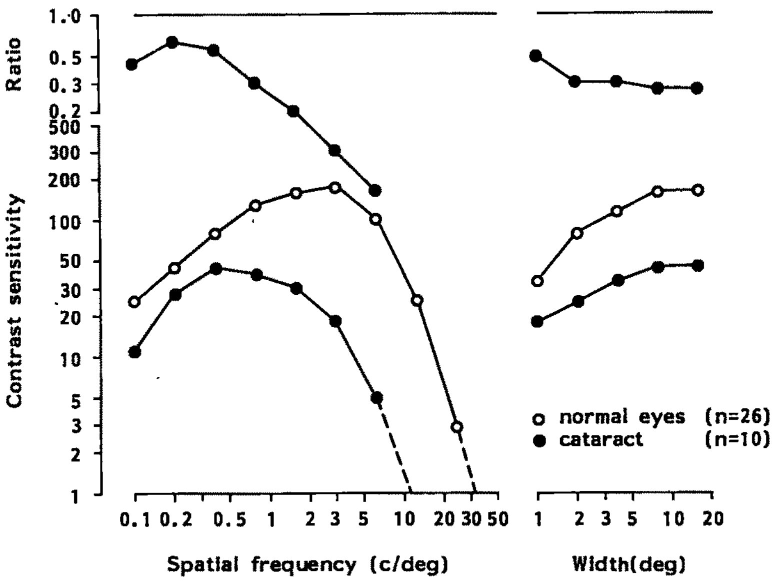

Fig. 3 Lower left: *Averaged CSFs for 26 normal and 10 cataractous eyes.* Lower right: *Width dependence for the same groups.* Upper: *Ratio curves with the normal curve as the reference.*

The averaged results for the two subgroups of eyes with optic nerve degeneration are shown in Fig. 2; the CSF for the normal group is given as a reference. The CSs for both optic nerve degeneration subgroups were lower than for the normal group at all spatial frequencies. For both subgroups the CS in the low spatial frequency range (CS(LF)) was reduced by about the same amount, while the CS(HF) was lower in the low vision subgroup than in the subgroup with normal visual acuity. The calculated grating acuity values were 0·71 and 1·01 respectively. The corresponding visual acuities were 0·49 and 1·14. In both subgroups the width dependence (see right-hand graph) had a similar form to that in the reference group, but the whole curve was lower. This is to be expected from the lower CS value at 1·6 c/deg in the CSF. The results were almost the same among subgroups containing 23 cases of optic neuritis without and 19 cases of optic neuritis with multiple sclerosis. This is not shown here.

Comparison of the averaged results for the cataractous eyes with those of the normal group in Fig. 3 indicates a reduction in CS(HF). This was expected from the lower mean visual acuity in this group (0·45); the grating acuity (0·48) was in accordance with this.

On the basis of these results we can recognise at least three differences between some of the groups. These differences, which we shall study in further detail, can be seen in: (1) the discrepancy between the two types of spatial resolution estimate—visual acuity and grating acuity; (2) the dependence of the CS on the width of the stimulus; (3) the contrast sensitivity for the low spatial frequency range.

Discussion

VISUAL ACUITY AND GRATING ACUITY

The Snellen test of visual acuity (VA) is an important tool in ophthalmological practice. It is a measure of the performance of the visual system at high contrast, and it is claimed that it evaluates the patient's reading ability. It is expressed as the reciprocal of the minimum angle of resolution in minutes of arc. The grating acuity (GA) may also be expressed in the same units; half a cycle of the highest visible frequency is taken as the minimum angle of resolution. Some relationship between VA and GA may be expected, though the stimuli are different (respectively optotypes and gratings).

Our results indicate that there is a discrepancy between the two estimates for the spatial resolution. For the normal group and for the optic nerve degeneration subgroup with normal VA the VA is on average greater than the GA, while for the group of amblyopic eyes the VA is much lower than the GA. The VA is also lower than the GA for the low vision subgroup with optic nerve degeneration, albeit to a lesser extent. Only for the group of cataractous eyes are VA and GA nearly equal.

In this study it is not proved whether in amblyopia the GA is an overestimation of the real spatial resolution or the VA an underestimation. Levi and colleagues found identical differences[21 22] and suggest it is because amblyopic visual systems have edge sensitive mechanisms broader than normal.[23 24] In five amblyopic subjects we also determined the VA with single letters (Sheridan-Gardiner test), and in four of them this measure for VA coincided with the GA,

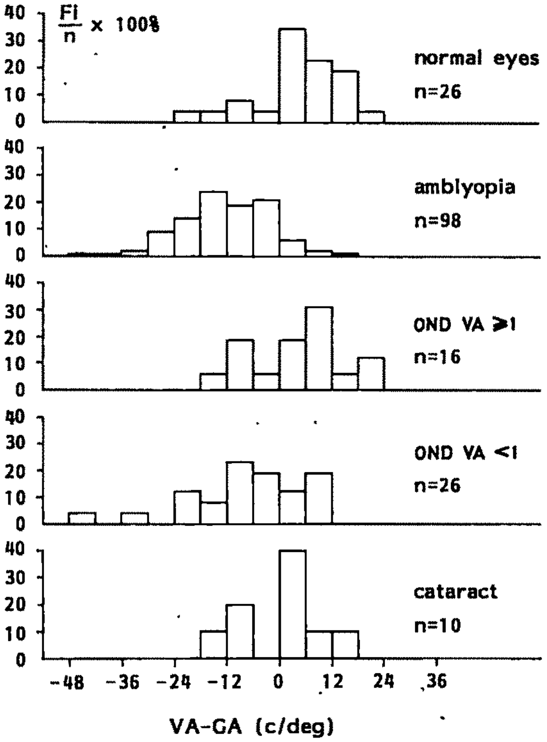

Fig. 4 *Frequency distribution of difference between visual acuity and grating acuity in the groups of normal, amblyopic, optic nerve degenerative (normal and low visual acuity), and cataractous eyes. The distributions are normalised to a total of 100%.*

though the values were still subnormal. This so called crowding phenomenon or separation difficulty[25 26] can be explained by the same edge sensitive mechanism.

The discrepancy between VA and GA (which is greatest in the amblyopia group) was further studied for its potential as a diagnostic measure. The discrepancy was expressed as the difference between VA and GA. Fig. 4 gives the frequency distributions of VA−GA for the groups of normal eyes and amblyopic eyes, for both subgroups of eyes with optic nerve degeneration, and for the group of cataractous eyes. Each distribution is normalised to a total of 100%. An analysis of variance[27] showed that the distributions cannot be regarded as samples from the same population: $F(4,175)=29{\cdot}7$; $p<0{\cdot}0001$. These results suggest that the VA−GA difference can be used to differentiate between some of the groups. By means of Tukey's multiple range test,[28] using $\alpha=0{\cdot}05$, it was found that the amblyopic group of eyes differs significantly from all the other groups of eyes except the low vision subgroup with optic nerve degeneration.

WIDTH DEPENDENCE

The second differentiating finding is the dependence of CS on the width of the stimulus. To detect a narrower grating more contrast is needed. In our experimental data the largest effect was found between 1° and 2° width. To obtain a statistical spread the slope S was calculated for the range from 1° to 4°. The slope is much higher for amblyopic eyes than for non-amblyopic eyes, as shown in Figs. 1 to 3.

An explanation for differences in width dependence between amblyopic and other eyes may be found in an influence of the sharp luminance discontinuity on the contrast needed for perception of the grating when the edges of the narrowing stimulus approach each other. It is not known whether the edge sensitive mechanism of Levi *et al.*[24] is sufficient as an explanation for the higher slope S in amblyopia, as the former seemed to play a part at approximately 10 min of arc, while the effect in the latter already happens at a half width of 120 min of arc. If an edge sensitive mechanism explains differences in VA−GA as well in width dependence among several groups of eyes, then there must be a correlation between the two variables. Indeed for the groups of 26 normal and 98 amblyopic eyes there is a significant correlation between VA−GA and the slope S (using $\alpha=0{\cdot}05$), though the association is weak ($r=-0{\cdot}39$). Research in this field is continuing.[29]

Fig. 5 gives the normalised frequency distributions for width dependence for all five groups. It is evident that the width dependence distribution for amblyopic eyes lies to the right, whereas the one for cataractous eyes lies to the left, with the other distributions somewhere between. There is a considerable overlap.

The result of the analysis of variance revealed a statistically significant difference between the groups: $F(4,175)=21{\cdot}0$; $p<0{\cdot}0001$. This suggests that the slope can also be used for differentiating between amblyopia and the other groups. Tukey's multiple range test indicated a significant difference (using $\alpha=0{\cdot}05$) between the amblyopic group of eyes and all other groups.

CONTRAST SENSITIVITY FOR THE LOW SPATIAL FREQUENCY RANGE

The two differences already discussed were between the amblyopia group and the other groups. A third clear difference can be found between both optic nerve degeneration subgroups and the other groups of eyes. Fig. 6 gives the normalised distributions of the contrast sensitivity for the low spatial frequency range (CS(LF), calculated as the mean of the CSs for 0·1, 0·2, and 0·4 c/deg) for the five groups. It is clear that the distributions for normal and amblyopic eyes do not greatly differ, while the optic nerve degener-

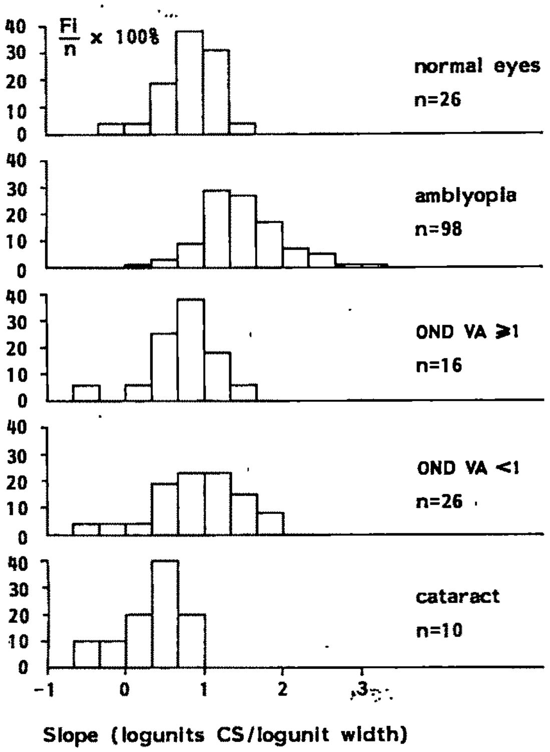

Fig. 5 *Normalised frequency distribution for the width dependence of contrast sensitivity; further as Fig. 4.*

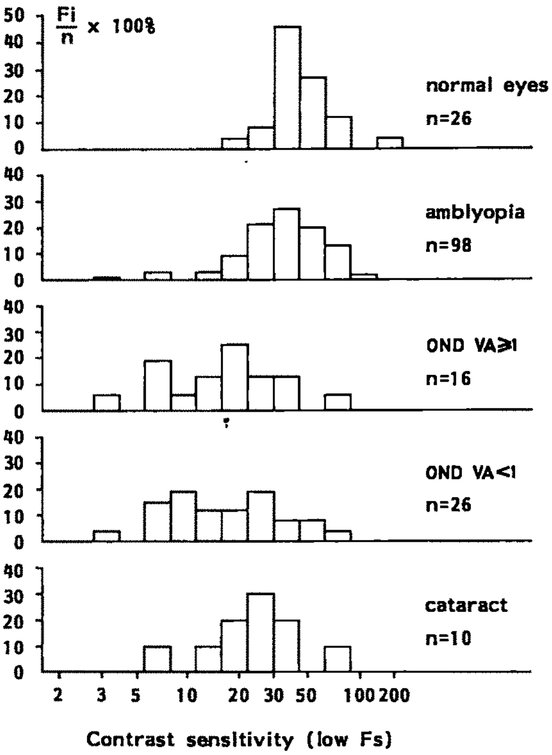

Fig. 6 *Normalised frequency distribution for contrast sensitivity at low spatial frequencies; further as Fig. 4.*

ation subgroups in general have lower values, though there is a certain overlap with the other groups. It is a common finding that some cases of optic neuritis or multiple sclerosis show decreased CS for only low, middle, or high spatial frequencies, or for combinations.[4,5,10] The cataract group is somewhere in between; the distributions in Fig. 6 show that the one for cataract is not bimodal and so does not support the two-type classification of Hess and Woo.[13] Inspection of the individual CSFs of cataractous eyes shows that low CS(LF) in this group may be due to the fact that in a considerable number of cases the CS(HF) was decreased to such an extent that not only the high frequency range but also the low frequency range was affected. Further, for the group of amblyopic eyes we did not find a bimodal distribution of CS(LF), as Hess and Howell postulated.[2]

The analysis of variance indicates a significant difference between the groups: F(4,175)=16·2; $p<0{\cdot}0001$. The fact that the optic nerve degeneration subgroups with both normal and low VA had decreased CS(LF) (Fig. 2) is an indication that this difference is typical of optic nerve degeneration, and hence can be used in the differential diagnosis between amblyopia and optic nerve degeneration. Tukey's multiple range test not only showed significant differences (using $\alpha=0{\cdot}05$) between both optic nerve degenerative subgroups on the one hand and the groups with amblyopic and normal eyes on the other, but also that the CS(LF) for cataractous eyes was significantly lower than for normal eyes.

COMBINATION OF FINDINGS

Each of the three variables so far described can be used to differentiate between different visual defects. We investigated the diagnostic value of combining the three variables in one test to differentiate between some of the groups, as stated in the introduction: (1) between amblyopia and optic nerve degeneration with low visual acuity; and (2) between normal eyes and optic nerve degeneration with normal vision. We used logistic discriminant analysis[28] to answer the two questions.

Diagnosis on the basis of our chosen variables was compared with the known, correct diagnosis (as determined by a complete examination). The results for the differentiation between amblyopia and low vision optic nerve degeneration are depicted in Fig. 7. It shows the ROC curve, which is the relationship between the percentage of correctly diagnosed

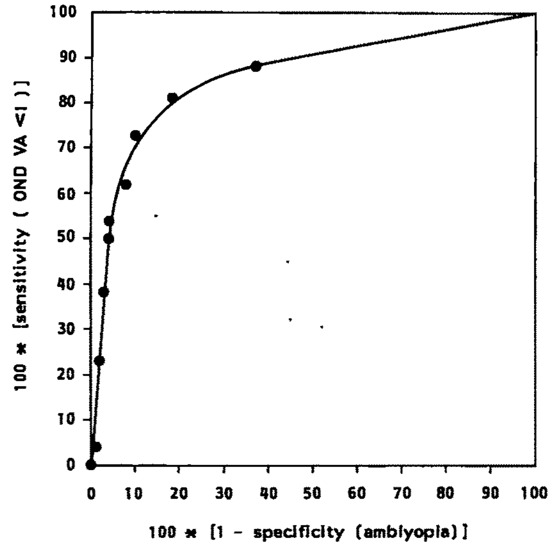

Fig. 7 *ROC curve showing, for the combination of the three variables, the relationship between the diagnostic sensitivity for optic nerve degeneration with low visual acuity and the diagnostic specificity for amblyopia.*

Table 1 *Results of logistic discriminant analysis for the group of amblyopic eyes and for the low vision optic nerve degeneration (OND) subgroup for a specific choice (see text)*

Diagnosis resulting from tests	*Known diagnosis*		
	OND (VA<1)	*Amblyopia*	*Total*
OND	21	18	39
Amblyopia	5	80	85
Total	26	98	124

optic nerve degeneration cases (sensitivity of the tests), and the percentage of incorrectly diagnosed amblyopia cases (1−specificity). The curve shows that if one chooses limits which ensure that the sensitivity is high (that is, many cases of optic nerve degeneration are diagnosed correctly) specificity is low (that is, many amblyopia cases are erroneously classified as optic nerve degeneration).

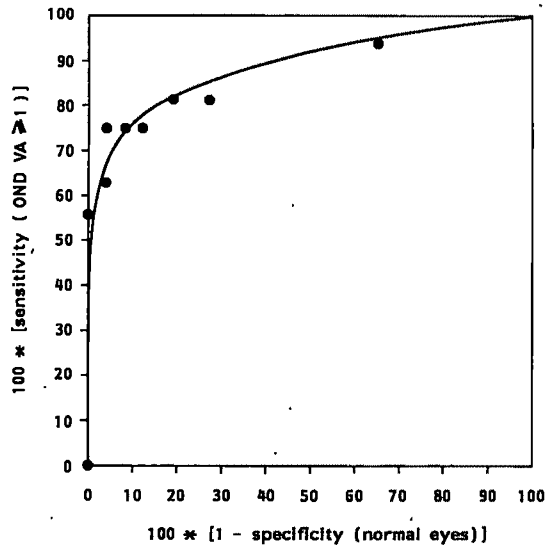

Fig. 8 *ROC curve showing, for the combination of the three variables, the relationship between the diagnostic sensitivity for optic nerve degeneration with normal visual acuity and the diagnostic specificity for normal eyes.*

The clinician has to decide whether it is acceptable to miss a number of amblyopia cases in order to obtain correct diagnosis for a greater proportion of optic nerve degeneration cases. Table 1 gives one example of such a choice, in which both the sensitivity and the specificity are about 80%. This choice corresponds to the following linear combination of the three variables discussed above:

$$Z=6{\cdot}7+0{\cdot}05*(VA-GA)-0{\cdot}18*CS(LF)-0{\cdot}4*S.$$

Whenever $Z>-1{\cdot}4$ the patient is assigned to the optic nerve degeneration group, otherwise to the amblyopia group. By means of this choice it turns out that a correct diagnosis is made in 80/98 or 82% of the amblyopes and in 21/26 (81%) of the optic nerve degeneration group, while an erroneous decision was taken in 23 out of 124 cases (19%). The predictive value of the test for amblyopia is high: 80/85 or 94%. For optic nerve degeneration the predictive value is considerably lower: 21/39 or 54%. Of course these last values depend on the incidences of the two types of disorders in the tested population.

In a similar way results for the comparison between the optic nerve degeneration subgroup which has normal VA and the group of normal eyes are given in Fig. 8 (ROC curve) and Table 2 (result of logistic discriminant analysis). If limits for normal tests are chosen so that 95% of the 26 normal eyes can be considered as such, it turns out that 12 out of 16 cases of optic nerve degeneration with normal vision (75%) are not assigned to the normal group despite the normal VA.

Table 2 *Results of logistic discriminant analysis for the group of normal eyes and for the optic nerve degeneration (OND) subgroup with normal visual acuity for a specific choice (see text)*

Diagnosis resulting from tests	*Known diagnosis*		
	OND (VA≥1)	*Normal eyes*	*Total*
OND	12	1	13
Normal eyes	4	25	29
Total	16	26	42

CONCLUSIONS

In the introduction several questions were raised which we can now answer.

The shape of the spatial contrast sensitivity function is partly related to the type of pathology. Specific for amblyopia is a discrepancy between visual acuity and grating acuity (VA<GA), in addition there is a strong dependence of contrast sensitivity on the width of the stimulus. In optic nerve degeneration there is a decreased contrast sensitivity in the low spatial frequency range; this happens in equal amounts in cases with decreased and with normal visual acuity. It is also found in a part of the group of cataractous eyes.

Decreased contrast sensitivity in the higher spatial frequency range occurs in all kinds of disorders of the visual system and is associated with reduced visual acuity (subject to the limitations expressed above for the group of amblyopic eyes).

The differences between the groups give valuable tests for the differentiation not only between amblyopia and optic nerve degeneration associated with reduced visual acuity, but also between optic nerve degeneration with normal visual acuity and normal eyes.

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Bupivacaine and lignocaine for ophthalmic surgery

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SUMMARY Bupivacaine 0·5% when used as a local anaesthetic for ocular cataract surgery does not give absolute ocular akinesia but provides adequate and prolonged pain relief. In comparison lignocaine provides good ocular akinesia at operation but pain relief is short lived. The mixture of the two local anaesthetics in equal volumes eliminated the disadvantages of their individual use.

General anaesthesia has replaced local anaesthesia in ophthalmic surgery for a number of reasons; patient co-operation is not required, delicate and prolonged surgery can be undertaken, and there is no risk of retrobulbar haemorrhage. It requires special equipment and preparation of the patient, and care and specialist anaesthetists that may not be available in developing countries. Local anaesthesia with either of the amides lignocaine or bupivacaine (Fig. 1) still has a place in the choice of anaesthetic for a poor risk patient. With the availability of a long acting drug such as bupivacaine, prolonged surgery can be performed,[1-3] and postoperative analgesia is assured.

In the present study the adequacy of analgesia, operating conditions, and complications were compared for three drug regimens under standard operating conditions. The retrobulbar block was performed with either lignocaine or bupivacaine or a mixture of lignocaine and bupivacaine according to a predetermined protocol.

The success of any nerve block depends on the operator, who requires a thorough knowledge of the anatomy. Diffusion of drugs is restricted by anatomical boundaries, and correct placement of drugs leads to a smaller dose being necessary. The study was therefore designed for blocks to be performed solely by the operator, so as to use the minimal doses of the various local anaesthetics to give acceptable ocular anaesthesia and akinesia.

Material and methods

Ninety adult consenting patients were allocated randomly to one of three groups (A, B, and C), 30 patients in each group. Group A had their cataract surgery performed under bupivacaine as the local anaesthetic. Group B had their cataract surgery under lignocaine, and in group C a mixture of lignocaine and bupivacaine was administered.

Each patient received 75 mg of pethidine intramuscularly one hour preoperatively to provide minimal sedation and analgesia. Thirty minutes before surgery each patient also received topical drops of 0·4% oxybuprocaine to the eye for surgery every 5 to 10 minutes till the operation began.

Group A patients received 1·5 ml of 0·5% bupivacaine through a retrobulbar needle, 4·0 ml of 0·5% bupivacaine at the stylomastoid foramen and around the parotid distribution of the facial nerve for the seventh cranial nerve block, and 0·5 ml of 0·5% bupivacaine each to the upper and lower lids for paralysis immediately before surgery.

Similarly, group B patients received 1·5 ml of 2% lignocaine retrobulbarly, 4·0 ml of 2% lignocaine for the facial nerve block and 0·5 ml of 2% lignocaine each to the upper and lower lids.

For the group C patients a mixture of 0·5% bupivacaine 3·5 ml and 2% lignocaine 3·5 ml was used. The two were thoroughly mixed before the

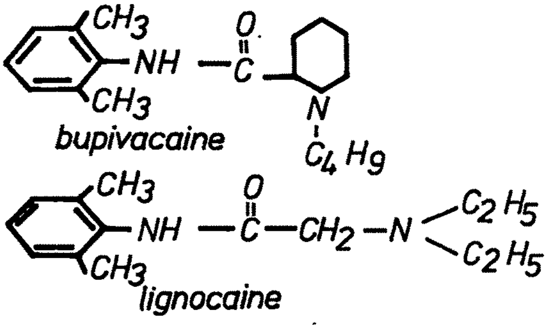

Fig. 1 Structural formulae of the amides *Bupivacaine and lignocaine*.

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injections were given. The retrobulbar injection was 1·5 ml of the mixture, 4·0 ml was used for the facial nerve block and 1·0 ml for the two lids.

All the patients used in this study had uncomplicated senile cataract which was extracted intracapsularly by the ab-externo incision. Cataract extraction was with the Amoilette cataract cryoprobe, and magnification was between 10 and 16 times under the Wild Heerburg M650 coaxial operating microscope. All procedures were standardised, and the first author performed all the surgery.

The presence or absence of ocular movements after each type of local anaesthetic was recorded by the naked eye and the operating microscope. In selected cases the eye movements were recorded with a video camera for subsequent study and classified as OVC/16a University of Jos and stored at the Medical Instructional Technology Unit. Records of eye movements were taken just before the placement of a superior rectus muscle suture and again after clearing the limbus, before the corneoscleral incision to enter the anterior chamber. After cataract extraction eye movements were further observed before reapposition of the corneoscleral wound and before the removal of lid sutures. Postoperatively the time each patient complained of pain necessitating relief with paracetamol was recorded, and the frequency of demand of postoperative pain relief was also recorded by the nurse.

Results

EYE MOVEMENTS

The results are recorded in Table 1. In Group A, who had bupivacaine alone, 37% of the patients had noticeable eye movements during surgery, both before and after cataract extraction, and these proved troublesome to the operator. Movements of this type occurred in 17% of patients who received lignocaine alone (group B), and in the same group just before removal of the lid sutures three patients developed a tremulous lower lid (muscle fasciculation) which did not interfere with the procedure. Almost all the patients in group C had akinesia before and after extraction of the cataract, except for two patients whose movements were so minimal that they were noticed only under the operating microscope at a moderate magnification of 16 times before the corneoscleral incision. These movements were abolished during the postcataract extraction periods of observation.

Table 1 *Frequency of eye movements, mild or moderate, in the three groups each with 30 patients*

	Group A (bupivacaine)	*Group B (lignocaine)*	*Group C (bupivacaine+ lignocaine)*
Moderate eye movements	11	5	0
Mild eye movements	0	3	2
Absolute akinesia	19	22	28
Totals	30	30	30

PAIN RELIEF

Groups A and C showed little demand for pain relief for up to 12 hours postoperatively (Table 2). By this time all the patients in group B, the group receiving lignocaine alone, had required analgesia. The group B patients who required analgesia in the first six hours received it two to three hours postoperatively.

COMPLICATIONS

There were no immediate or postoperative complications of the nerve block. All nerve blocks provided analgesia at the time of operation, and return of sensation occurred in all patients.

Discussion

Lignocaine and bupivacaine are both local anaesthetic amides but they differ in their physicochemical properties. Bupivacaine is highly protein bound, 94% being bound to plasma protein compared with 64% lignocaine at the same plasma concentration.[4] The long duration of action of bupivacaine has been related to its tissue binding properties.[5]

This study showed that for postoperative pain relief bupivacaine when used as a local anaesthetic for ocular surgery gives adequate and prolonged ocular analgesia. The use of lignocaine alone was associated with a rapid return of pain, and more than half of the patients in this group required analgesia within the first two to three hours after surgery.

The rate of onset of action of a local anaesthetic drug depends on its degree of ionisation at tissue pH, that is, its pKa. Lignocaine has a pKa of 7·87 and has a mean onset of action of three minutes because up to 30% may be in the non-ionised form. Bupivacaine has a pKa of 8·05, so that at tissue pH less of the drug is non-ionised (about 10%) and its duration of onset

Table 2 *Time after the operation when the first analgesia was administered to the patients, 30 patients in each group*

	Group A (bupivacaine)	*Group B (lignocaine)*	*Group C (bupivacaine+ lignocaine)*
Less than 6 hours	6	17	0
6 to 12 hours	0	13	6
More than 12 hours	24	0	24
Totals	30	30	30

of action is longer.[6] In this study the slow onset of action of bupivacaine did not affect the time for surgery to begin because the time between the block and the incision was dependent on other surgical factors.

Another difference between lignocaine and bupivacaine at the concentration used related to the quality of the block. Bupivacaine 0·5% is associated with a sensory block but the motor blockade is slight. The motor blockade is increased by increasing the concentration of bupivacaine,[7] but this solution was not available to the author. It was observed that in group A with bupivacaine alone there was adequate ocular analgesia but not absolute akinesia. The 0·75% bupivacaine concentration when administered alone[2] showed a delay in onset of akinesia of more than 15 minutes. Lignocaine when used alone gave better ocular akinesia, but pain relief was less effective.

The group C patients, who received a 50/50 volumetric mixture of bupivacaine and lignocaine, had the best results both for akinesia and for pain relief. The method minimised the disadvantages experienced in the use of these two local anaesthetic agents individually.

The use of adrenaline with the drugs was considered. Toxic effects are related to systemic absorption or accidental intravascular injection and for amide-amide mixtures are additive. Mixtures of lignocaine and bupivacaine are used for brachial plexus block and epidural block,[8] but no single mixture had been advocated. It has been established that 0·5% bupivacaine and 2% lignocaine with adrenaline give comparable blockades.[9] The addition of adrenaline to bupivacaine is not necessary to improve the nerve blockade, and the resulting pH of a solution with adrenaline is more acid, so that it has an even slower onset of action. The mixture chosen proved to be adequate, but a nerve blockade with a higher concentration of bupivacaine might have proved to be more suitable.

A bupivacaine and lignocaine mixture has been used in retinal detachment surgery[10] to give satisfactory operating conditions in 90% of cases. Its use in cataract surgery in this study, it should be noted, was with a small volume, 1·5 ml, injected through the retrobulbar needle and with a lower concentration than that used in other studies.[1-3]

We recommend the use of a 50/50 volumetric mixture of lignocaine and bupivacaine for ocular surgery in places where general anaesthesia is unavailable, dangerous, and costly.

We acknowledge the valuable assistance by both the theatre and ward nurses of the ophthalmic department and the technical aid from the Medical Instructional Technology Unit for the video records and the black-and-white prints. Finally we thank Mr Emmanuel Ikoroh for his secretarial assistance.

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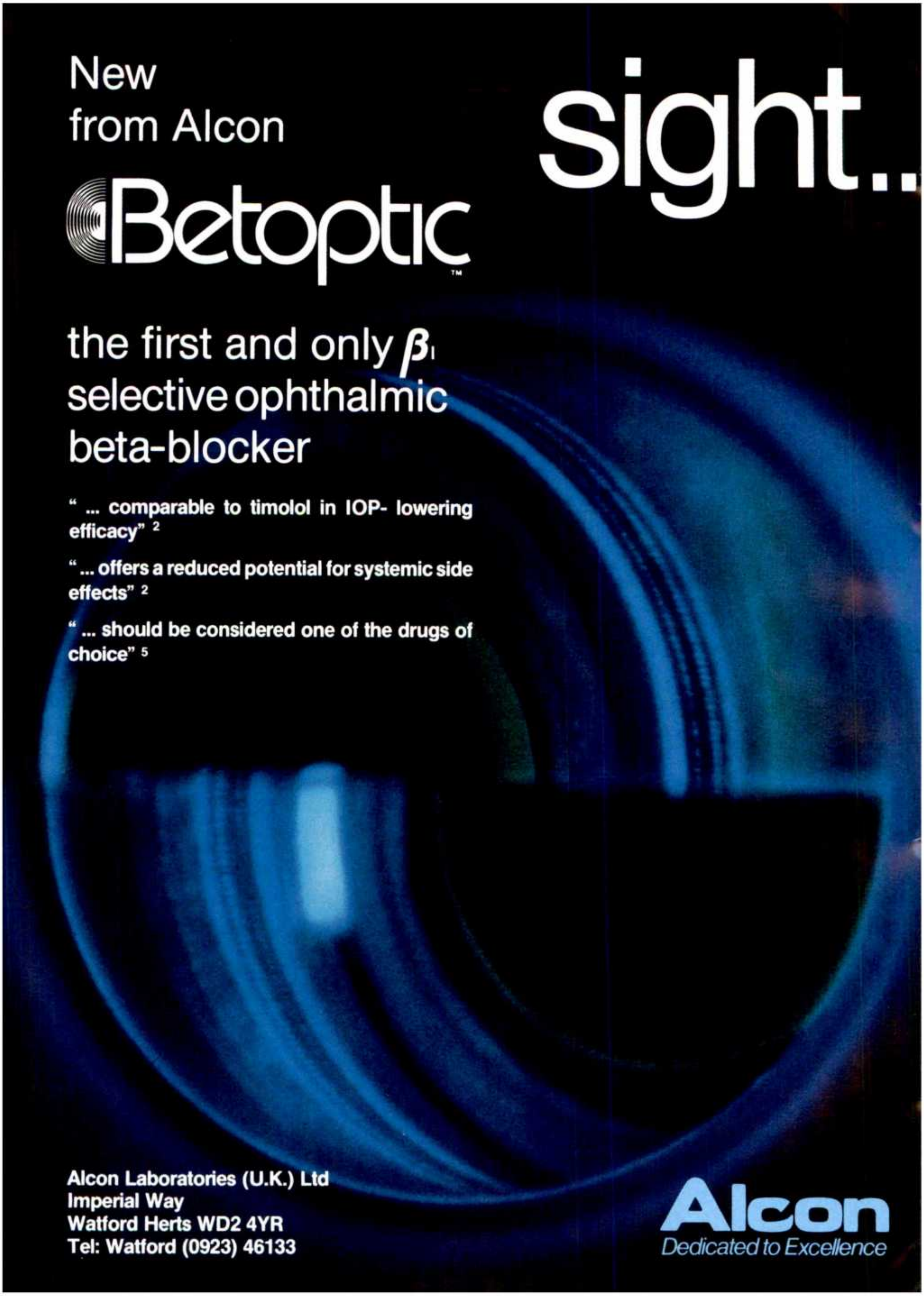

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Complete evulsion of the globe and optic nerve

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SUMMARY A 17-year-old boy had an evulsion of globe and optic nerve from an automobile accident. Computed tomography showed a severed optic nerve on the injured side. A visual field defect was demonstrated in the other eye.

Optic nerve injuries may occur from direct or indirect injuries to the orbital region.[1,2] An unusual case of evulsion of the globe and optic nerve with field defect in the other eye from an automobile accident is reported. The mechanisms, early diagnosis, and management of optic nerve injuries are discussed.

Case report

A 17-year-old boy was brought to the Emergency Room after an automobile accident. He was thrown through the windscreen of the car, approximately 20 feet (6 m) on to the pavement. The patient was unconscious and could be aroused to painful stimuli only. He had a closed head injury with cerebral oedema and acute respiratory distress syndrome, for which cricothyroidectomy was done. His right globe was outside the orbit with the lids tightly closed behind it (Fig. 1). Vision could not be assessed. On the right side there was marked lid oedema, the cornea was clear, the anterior chamber had a 25% hyphaema, and the pupil was 7 mm in size, round and non-reactive. There was no laceration of cornea or sclera. The fundus could not be visualised. The left eye was normal. A CT scan showed a small left subdural haemorrhage with cerebral oedema and shift of midline structures to the right. There was haemorrhage within the orbit posterior to the globe. The patient received intravenous mannitol, dexamethasone, frusemide, and cefapirin. Four hours after the accident a right lateral canthotomy was done, but the globe could not be reposited in the orbit. Two hours after treatment with ice packs and keeping the eye in a moist chamber the globe was reposited in the orbit with considerable difficulty, and a complete tarsorrhaphy was done.

For five days the patient was medically and neurologically unstable. He regained consciousness, and it was then found that he had no vision in the right eye. A day later he had tenderness over the right upper lid, and the possibility of an orbital abscess was entertained. He was transferred to the Ophthalmology Department. A CT scan of the orbit done at this time showed no haemorrhage or abscess within the orbit. However, there was evulsion of the optic nerve on the right side (Fig. 2). The tarsorrhaphy was then opened. There was no light perception in the right eye. The eye was proptosed and exotropic, with marked limitation of extraocular movements in all directions of gaze. There was blood staining of the cornea. Details of the anterior chamber and fundus

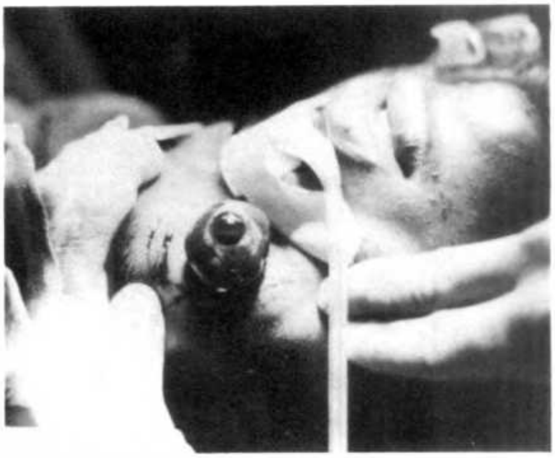

Fig. 1 *Appearance of the eye at initial presentation.*

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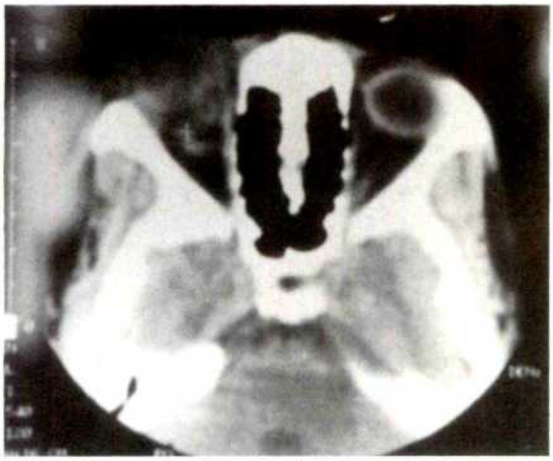

Fig. 2 *CT scan showing severed optic nerve on the right side.*

were not visible. The left eye had 20/20 vision and the examination gave normal results.

Fifteen days after the accident the right eye was enucleated. At surgery there was a horizontal laceration in the conjunctiva inferiorly 6–8 mm below the limbus extending across the whole length of the palpebral fissure. The inferior rectus muscle had been disinserted and was reattached to the globe 20 mm posterior to the limbus. The optic nerve had been transected 31 mm behind the globe. The postoperative course was uneventful. Goldmann perimetry in the left eye, done after surgery, showed a relative depression of I 2e and II 2e isoptres in the superior temporal quadrant (Fig. 3). The visual fields showed improvement when repeated after five months (Fig. 4).

Discussion

The word 'evulsion' stems from the latin 'e' (out) and 'vellere' (to pluck) and the word 'avulsion' is derived from the latin 'a' (away) and 'vellere'. These terms have been used interchangeably by most authors. Salzmann[3] defined 'avulsion' of the optic nerve as 'the forceful backward dislocation of the optic nerve from the scleral canal without any break in continuity of the adjacent coats of the globe.'

Lister[4] and Walsh and Hoyt[5] stated that the blow

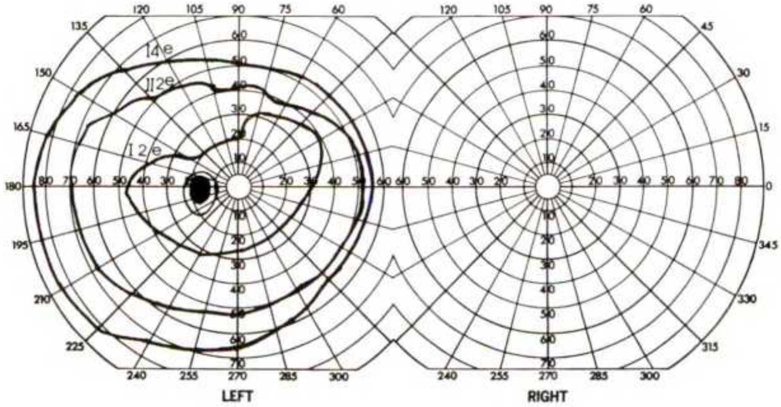

Fig. 3 *Visual fields at initial examination.*

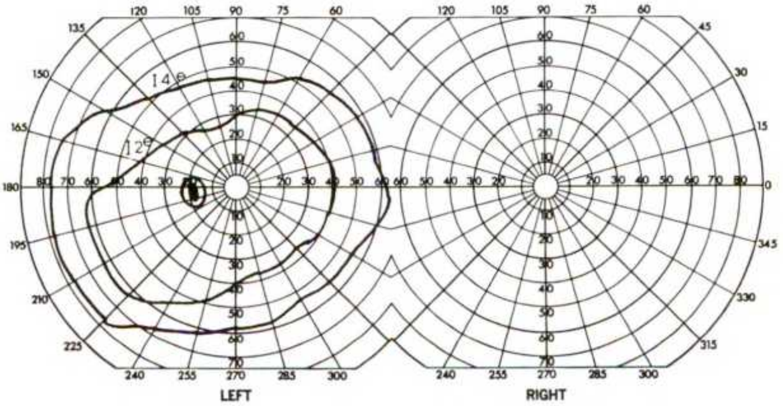

Fig. 4 *Visual fields at subsequent examination.*

on the front of the eye produced a sudden increase in intraocular pressure which ruptured the lamina cribrosa and expelled the nerve. Lowenstein[6] postulated that rupture of the optic nerve occurred at the lamina cribrosa because of anatomical weakness of that region. The posterior portion of the lamina cribrosa is one-third the thickness of the surrounding sclera, and the optic nerve fibres are not supported by myelin or connective tissue septa in this part of the nerve. He also noted that the optic sheath usually remained attached to the globe since it is more elastic than the optic nerve. Lagrange's[7] theory of optic nerve injury was that indirect facial injury set up concussion waves which travelled through the pterygo-maxillary fissure into the orbit and the globe was then propelled forward, stretching the nerve causing evulsion.

The optic nerve can be involved in injuries over the fronto-orbital region[8] or even after trivial injuries like a finger or stick entering the orbit tangentially, either penetrating or leaving the conjunctiva intact.[9-12] In Turner's[13] series the frequency of complete or incomplete injuries of the optic nerve was about 1·5%. Only injuries to the olfactory and facial nerves were commoner than those to the optic nerves. Damage to the optic chiasm can occur with fronto-orbital injuries. Traquair *et al.*[14] considered that with these injuries there was interruption of vascular supply to the chiasm. These vessels are attached to the base of the skull, and movement of the chiasm and brain could cause laceration or thrombosis, with subsequent softening of the chiasm. Trauma to the optic nerve can result in intrasheath haemorrhage, oedema, contusion, avulsion, or evulsion of the nerve. The visual loss might be sudden and permanent, sudden with gradual partial recovery, or chronic and progressive. Other ocular findings associated with optic nerve injury may be subconjunctival haemorrhage, limitation of extraocular movement, dilated fixed pupil, and proptosis. In avulsion of optic nerve the fundus may show haemorrhage fanning out from the disc, with an elliptical excavated defect in the disc. This defect would be later filled with gliotic tissue, which may extend into the vitreous. Extensive vitreous haemorrhage may delay or prevent the diagnosis in the early stages of optic nerve injury, and the later stages may be confused with a developmental anomaly.[15] Visual field defects may vary from concentric contraction to sectorial involvement.

The treatment of optic nerve injuries is controversial. Those who advocate massive dosage of steroids believe that it decreases the swelling of the optic nerve in the optic canal and thereby partly or completely restores vision. Panje *et al.*[16] recommend giving 1 mg Decadron (dexamethasone) per kg body weight initially, then 0·5 mg per kg every six hours for 24 hours, and then 1 mg per kg per day for one to two days. If no response occurs within 48 hours, therapy should be stopped. If the patient does respond, this dose is continued for five days and then rapidly tapered. If visual acuity fails while the patient is on steroid, Panje *et al.*[16] suggest operative intervention. Surgical intervention consists in decompression of the optic nerve, which can be achieved by transorbital, transethmoidal, or transantral approaches. Fukado[17] popularised the transethmoidal approach and had spectacular results with it. The decision to intervene surgically in optic nerve damage is a difficult one. Walsh and Hoyt[5] stated that, if the loss of vision or abnormal pupillary response to light developed within minutes after the injury, the possibility of surgical intervention should be considered in order to halt further visual deterioration.

Our patient sustained a severe concussive injury to the orbit. This probably resulted in forward propulsion of the globe, and the retrobulbar haemorrhage which occurred caused rapid proptosis. This may have resulted in the lids getting caught behind the globe. The laceration in the inferior conjunctiva, with disinsertion of inferior rectus, might have been caused by a sliver of glass from the windscreen. The optic nerve might have been cut by the same piece of glass, as the globe was suddenly pushed forwards, or it might have been evulsed. The site of injury as far back as the optic chiasm resulted in injury to the anterior loop of crossed fibres from the opposite nerve, causing a relative field defect in the superior temporal quadrant of the eye. Traquair *et al.*[14] considered that with fronto-orbital injuries there was movement of the chiasm and the brain, and this might have occurred in our patient. As the oedema round the chiasm subsided, the visual field in the left eye showed improvement.

To our knowledge no other case has been described in which an evulsion of the globe and optic nerve from the orbit resulted from trauma and field defects occurred in the other eye. The only analogy which can be drawn with our case is in cases of autoenucleation where the globe and optic nerve have been evulsed from the orbit, resulting in visual field defect in the remaining eye. In the case of Krauss *et al.*[18] there was a 44 mm attached segment of the optic nerve, and the patient had temporal hemianopsia of the remaining eye. The diagnosis of injuries to the optic nerve by either direct or indirect trauma depends on careful examination of visual acuity, the visual fields, and the pupillary reflexes. Frequent evaluation of visual acuity is necessary to decide if surgical intervention is required. The role of massive dose of steroids in reversing optic nerve damage is controversial.

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A comparison of cycloplegic and manifest refractions on the NR-1000F (an objective Auto Refractometer)

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SUMMARY The manifest (dry) and cycloplegic refractions of 50 eyes of 25 patients aged 8 to 28 years were studied on the Nikon Auto Refractometer NR-1000F (AR) and compared with the results of clinical refraction (CR) under homatropine and the final clinical acceptance on postmydriatic testing. Only patients in the younger age groups with low to moderate refractive errors were included in this study; high myopes and hypermetropes and patients with aphakia and mixed astigmatism were excluded. The degree of agreement for spherical equivalents, sphere components, and cylinder components was analysed separately for both cycloplegic and manifest refractions on the AR and CR. The results showed that the fixation target in the NR-1000F induces significant instrument myopia during manifest refraction in the younger patients with lower refractive errors. We recommend that caution should be exercised in interpreting manifest refractions on the AR, especially in younger patients. A cycloplegic automatic refraction would be acceptably accurate.

In a previous study[1] the manifest (dry) refraction of 165 eyes of 86 patients, aged 6 to 75 years, was studied on the Nikon Auto Refractometer NR-1000F. The results obtained were compared with those from clinical refraction and analysed for degree of agreement of various refractive components in different types and grades of refractive errors in the separate age groups.[1]

Though determination of the cylinder axis was found to be very reliable on the NR-1000F Auto Refractometer (AR), the spherical and cylindrical components and the spherical equivalents were observed to skew towards more minus (or less plus), especially so in emmetropes, low hypermetropes, and low myopes. This error in manifest refraction on the AR was observed to decline with increasing age over 40 years, and it was also significantly lower in aphakia and mixed astigmatism.[1]

It thus seemed that in spite of the obvious utility of the device its inbuilt automatic fogging system does not adequately neutralise the patient's accommodative efforts, the fixation target probably inducing significant instrument myopia.[1] Hence to test our suspicions we undertook the present study comparing the clinical and AR data on eyes under the effect of cycloplegia.

Materials and methods

The principles and steps of operating the NR-1000F Auto Refractometer have been outlined previously.[1] Further operating and maintenance information is given in the manufacturer's instruction manual.

A total of 50 eyes in 25 patients were selected for this comparative analysis. Their ages ranged from 8 to 28 years (Table 1). Except for only two patients who were medical staff, all the other patients in the study were those attending the outpatient department of our hospital for refractive problems. Only patients in the younger age groups with low to moderate refractive errors were included; high myopes and hypermetropes, and patients with aphakia and mixed astigmatism were excluded.

All refractions on the AR were performed with and without the effect of cycloplegia. The cycloplegic used was adequate instillation of homatropine 2% drops in all the eyes. Clinical refractions were carried out under cycloplegia only, together with a subjective acceptance determined under homatropine. A post-

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Table 1 *Distribution of 25 patients (50 eyes) by refractive error and age*

Age group (years)	*No. of patients*	*Type of refractive error (no. of eyes)*			*No. of eyes*
		Myopia	*Hypermetropia*	*Emmetropia*	
<10	1	2	0	0	2
11–20	14	12	8	8	28
21–30	10	6	2	12	20
Total	25	20	10	20	50

mydriatic test was undertaken a week later in accordance with the guidelines routinely followed in clinical refractive practice.

The final prescriptions were based on the objective and subjective clinical data under homatropine and the subjective acceptance by the patient in the postmydriatic test.

The subjective acceptance determined clinically under cycloplegia (CRc) was compared with the AR printout data also under cycloplegia (ARc). The manifest refraction AR printout data (ARm) were similarly matched with the final clinical prescription (CRm). The ARm−ARc and CRm−CRc were also calculated for the various refractive components.

The refractive errors in all the eyes were determined clinically as well as on the AR but, as in our previous study,[1] not necessarily by the same examiner. Whenever both the tests were conducted by the same person, the clinical refraction was invariably done first, so as to obviate any possible examiner bias in the clinical refractive data.

A minimum of three AR readings were obtained for each eye tested, and the reading with the maximum confidence value in each eye was selected for comparison. Readings with a confidence value of less than 90 were rejected as advised in the operating manual instructions.

Results

The distribution of all the 25 patients by refractive error and age is given in Table 1. Eleven were males and 14 females.

The cylinder axis data determined on AR were as clinically reliable and accurate as found in our previous study on manifest refraction.[1] Hence the detailed comparative analysis for degree of agreement for cylinder axis is not presented any further.

The mean differences and standard deviations (SD) between Auto Refractometer (AR) and clinical refraction (CR) readings in spherical equivalent data, sphere components, and cylinder components are shown in Table 2, both under cycloplegia and manifest conditions separately. The percentage agreements for the different refractive components are analysed in Table 3, again separately for the cycloplegic and manifest refractions.

The means of the differences between ARm and ARc, and CRm and CRc, for the various refractive components are evaluated in Table 4.

Discussion

As our present study has confirmed our earlier observations on the reliability of cylinder axis readings on the AR with or without cycloplegia, we have omitted the presentation of these data, and have focused our attention here on the spherical and cylindrical power data under manifest and cycloplegic conditions.

Our observations in this younger age group depicted in Tables 2 and 3 amply bear out our earlier suspicion[1] that the inbuilt automatic fogging system of the NR-1000F fails adequately to neutralise the patient's accommodative efforts during manifest refraction, though this problem declined with increasing age over 40 years and hardly existed in aphakia, mixed astigmatism, and higher refractive errors—all conditions in which the patient did not wish to or could not accommodate significantly.[1]

Perrigin *et al.*[2] had also suggested that the inclusion of younger subjects would lower the extent of agreement between the clinical and automatic refractions on their subjective refractometer (SR III). Another study[3] of the effect of cycloplegia on the determination of refractive error by an objective autorefractometer (Ophthalmometron) did not show instrument myopia to be significant. Our clinical refractive

Table 2 *Mean differences and standard deviations between Auto Refractometer and clinical refractive data (50 eyes)*

	Cycloplegic (c) readings (ARc−CRc)			*Manifest (m) readings (ARm−CRm)*		
	Spherical equivalent (D)	*Sphere component (D)*	*Cylinder component (D)*	*Spherical equivalent (D)*	*Sphere component (D)*	*Cylinder component (D)*
Mean*	−0·02	−0·03	−0·02	−0·92	−0·90	−0·22
SD	0·25	0·24	0·34	0·90	0·97	0·46

*The minus (−) sign indicates more myopia or less hypermetropia on the NR-1000F (AR) than by clinical refraction (CR).

Table 3 *Percentage agreement between Auto Refractometer and clinical refractive data of various refractive components (50 eyes)*

	Spherical equivalent (D)			*Sphere component (D)*			*Cylinder component (D)*		
	±0·25	*±0·5*	*±1·0*	*±0·25*	*±0·5*	*±1·0*	*±0·25*	*±0·5*	*±1·0*
Cycloplegic readings (ARc and CRc)	86%	96%	100%	80%	100%	100%	78%	92%	100%
Manifest readings (ARm and CRm)	32%	44%	68%	34%	54%	70%	64%	70%	90%

Table 4 *Mean differences and standard deviations between cycloplegic and manifest refractive data (50 eyes)*

	Auto Refractometer (AR) readings (ARm–ARc)			*Clinical refraction (CR) readings (CRm−CRc)*		
	Spherical equivalent (D)	*Sphere component (D)*	*Cylinder component (D)*	*Spherical equivalent (D)*	*Sphere component (D)*	*Cylinder component (D)*
Mean*	−1·19	−1·10	−0·20	−0·32	−0·28	−0·03
SD	0·90	0·91	0·38	0·22	0·22	0·09

*The minus (−) sign indicates more myopia or less hypermetropia in the manifest readings (m) than cycloplegic readings (c).

results under manifest and cycloplegic conditions show that the difference between CRm and CRc is in broad agreement with the known differences reported earlier by means of conventional techniques.[3,4] Theoretically, ARm−ARc should be equal to CRm−CRc. However, the difference between ARm and ARc was much higher than CRm−CRc in our study, as is clear from Table 4 ('higher' denoting a larger skew towards more minus or less plus). Again, a significant difference was observed between ARm and CRm (Tables 2 and 3), whereas ideally there should not be any difference at all, and ARm should be equivalent to CRm. But, as ARc was virtually identical with CRc (Tables 2 and 3), we cannot but conclude that the fixation target in the NR-1000F induces significant instrument myopia during manifest refraction in the younger patients with lower refractive errors.

We strongly suggest that automatic refractors like the NR-1000F should be used with great caution when determining manifest refractions, especially in younger patients in whom accommodation is more active than in older, for significant instrument myopia may be induced by the device. A cycloplegic refraction in these eyes would afford acceptably accurate baseline refractive data as a guideline for clinical prescription. Of course the manifest readings on the NR-1000F have proved to be much more reliable in cases of aphakia, mixed astigmatism, and high refractive errors, and for the determination of cylinder axes in all cases.

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British Journal of Ophthalmology, 1987, **71**, 76

Book reviews

Ophthalmology. Pocket Picture Guides Series. By Colin M Kirkness. Pp. 83. £4·95. Gower: London. 1985.

It is difficult to target the group of readers who would most benefit from this excellent little pocket book of ophthalmology colour pictures. Pocket diary size and 83 pages, it is one of a series of such guides. It consists of a selection of colour photographs, and a few diagrams, of ophthalmological conditions. Almost all the photographs are of high quality and the corneal conditions are especially well depicted, with the exception of pterygium, which is an atypical example. The illustration of buphthalmos is also unsatisfactory, as it shows a rather distant view of an established case with a totally scarred cornea, and the glaucoma disc photograph is somewhat blurred.

Each photograph has an enlarged caption, but of course this cannot be regarded as a text; therefore written information is necessarily slight. Although not comprehensive, this guide has a good range of conditions well illustrated, and the pictures of squint are especially useful. Probably the most effective readership for this book would be informed physicians and general practitioners, for it is an easily carried little ready reference volume.

JAMES L KENNERLEY BANKES

Chandler and Grant's Glaucoma. 3rd Edn. Edited by D. L. Epstein. Pp. 539. US $60·50. Lea and Febiger: Philadelphia. 1985.

The book is divided into four parts. The first, which is introductory, starts with an excellent section on general considerations including remarks about common symptoms, external influences, including various medicines, and borderline cases with characteristics warning of the possibility of future glaucoma. The remainder of the introductory section gives good advice about the examination of the eye in glaucoma, when to start treatment, and the uses of lasers.

Then follow the three main sections of the book, and multiple authors participate in these. Part 2 deals with the diagnosis and treatment of an extensive range of types of glaucoma, and it is of interest that a special section is allotted to progressive low-tension glaucoma, that most enigmatic manifestation of the disease. Part 3 deals with surgery and its implications and part 4 with the childhood glaucomas.

The book is beautifully presented, clearly written, and has of course an impeccable pedigree. The new principal editor gracefully acknowledges his debt to the two original masters, Chandler and Grant, and is a worthy successor to them.

REDMOND J H SMITH

Documenta Ophthalmologica Proceedings Series 43. Second European Glaucoma Symposium Helsinki, May 1984. Eds. E. L. Greve, W. Leydhecker and C. Raitta. Pp. 364. £55·50. Junk: Netherlands. 1985.

Researchers in glaucoma, as in other subspecialties in ophthalmology, may be likened to ants all working away at their chosen site. These workers pursue plans parallel to or divergent from those of other researchers. Every few years the temptation arises to make them down tools and assemble at a convivial spot for a rest, an exchange of ideas and charging of the mental batteries. This period provides an opportunity to swap work stories and assess progress reports. To prevail on worker ants to stop and assemble in this way the temptation must be great. All credit then to Christina Raitta and her colleagues on organising the Second European Glaucoma Symposium at Helsinki held in May 1984. To judge from the number of reports included in these proceedings of the Second European Glaucoma Symposium the venue was tempting indeed. The speakers frequently came from outside Europe, making the meeting truly international.

These proceedings of the Second European Glaucoma Symposium (the first was held in Brighton four years before) can only reflect the bare bones of the meeting. Much of the information exchanged in meetings such as this occurs in the discussion after and around each paper, though such discussions go unreported here.

In reviewing these proceedings a number of topics stand clear of the field. Computerised perimetry is the glaucoma test of the moment and promises to provide a far better follow-up for our glaucoma patients. Flammer suggested, however, that both focal and diffuse loss of visual function could occur in glaucoma (meaning that our conventional visual field tests are only picking up focal visual loss). This possibility could explain the difference in the appearance of the optic disc in different types of glaucoma and the sometimes anomalous and bizarre contrasts in hue discrimination seen in patients with ocular hypertension and glaucoma.

Many beta blockers are trying to assault the timolol citadel, so far without success. The proceedings suggest that this may change. Laser trabeculoplasty continues to attract interest, though none of the papers reported here show really long term results. This is of importance in view of the recent suggestion that the hypotensive effects of laser trabeculoplasty diminish in the long term. Surgical treatment fared better, for two 10-year follow-up studies showed that continued long term intraocular pressure control should be maintained.

As in all meetings such as this the quality of papers reported was variable. There can be little doubt, however, that the workers attending could have only learnt from each other as we learn from them. These proceedings are a useful update over many glaucoma subjects, making worthwhile reading for those with an interest in the subspecialty.

ROGER A HITCHINGS

Notes

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The Fifth Congress of the European Intraocular Implantlens Council will be held in Jerusalem, Israel, on 13–18 September 1987. Full details from the Congress Secretariat, PO Box 50006, Tel Aviv 61500, Israel.

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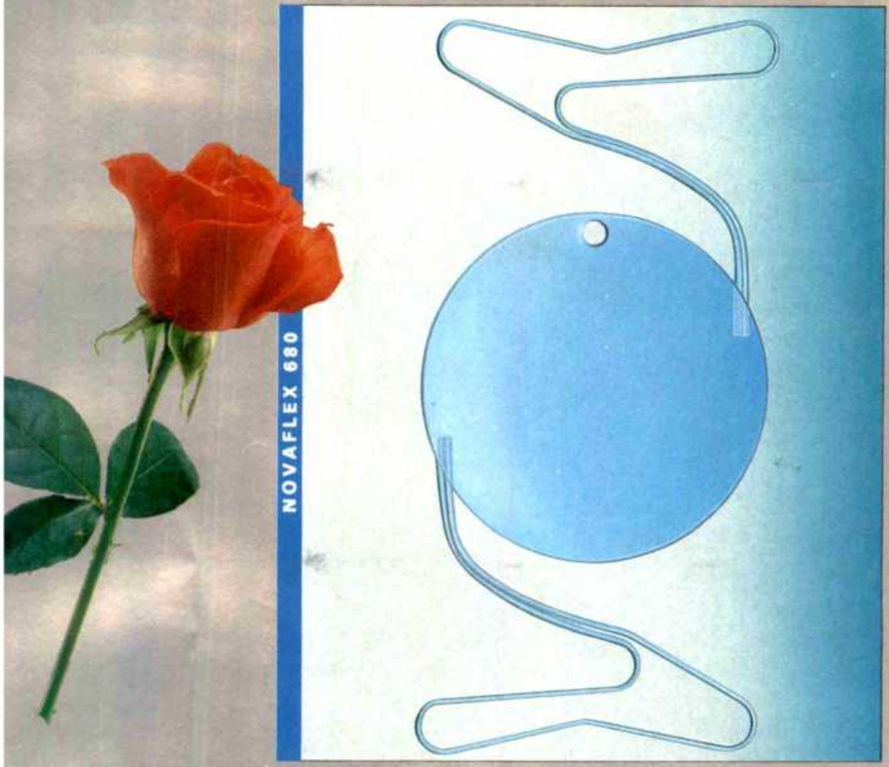

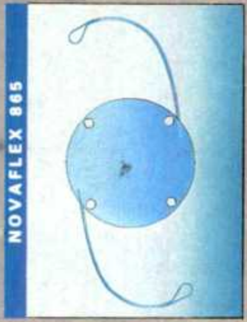

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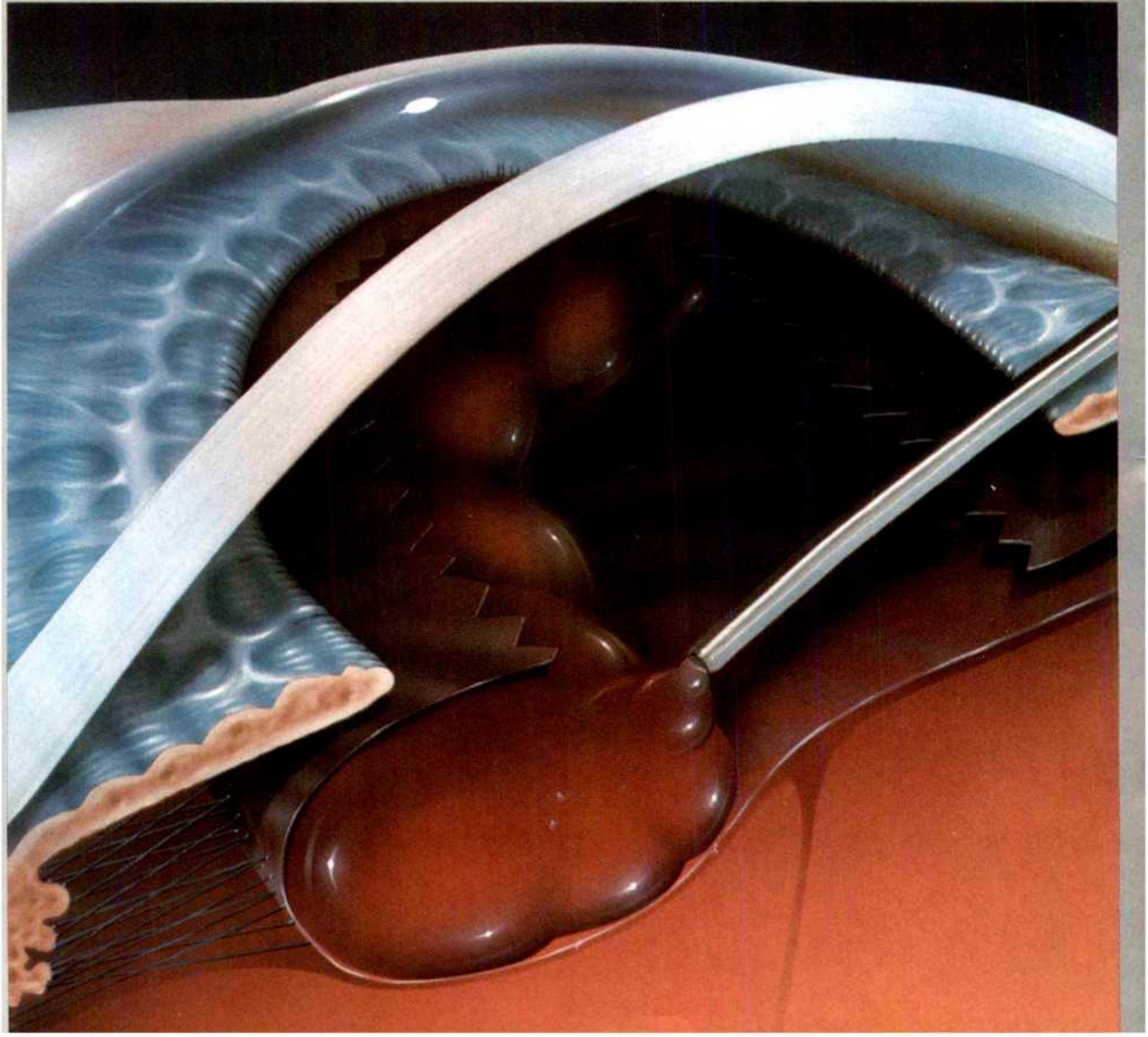

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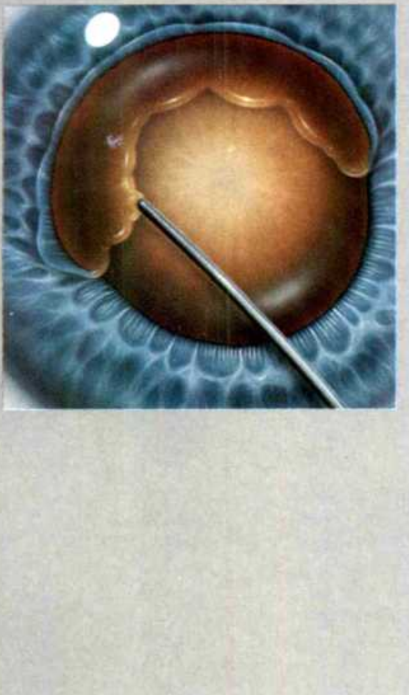

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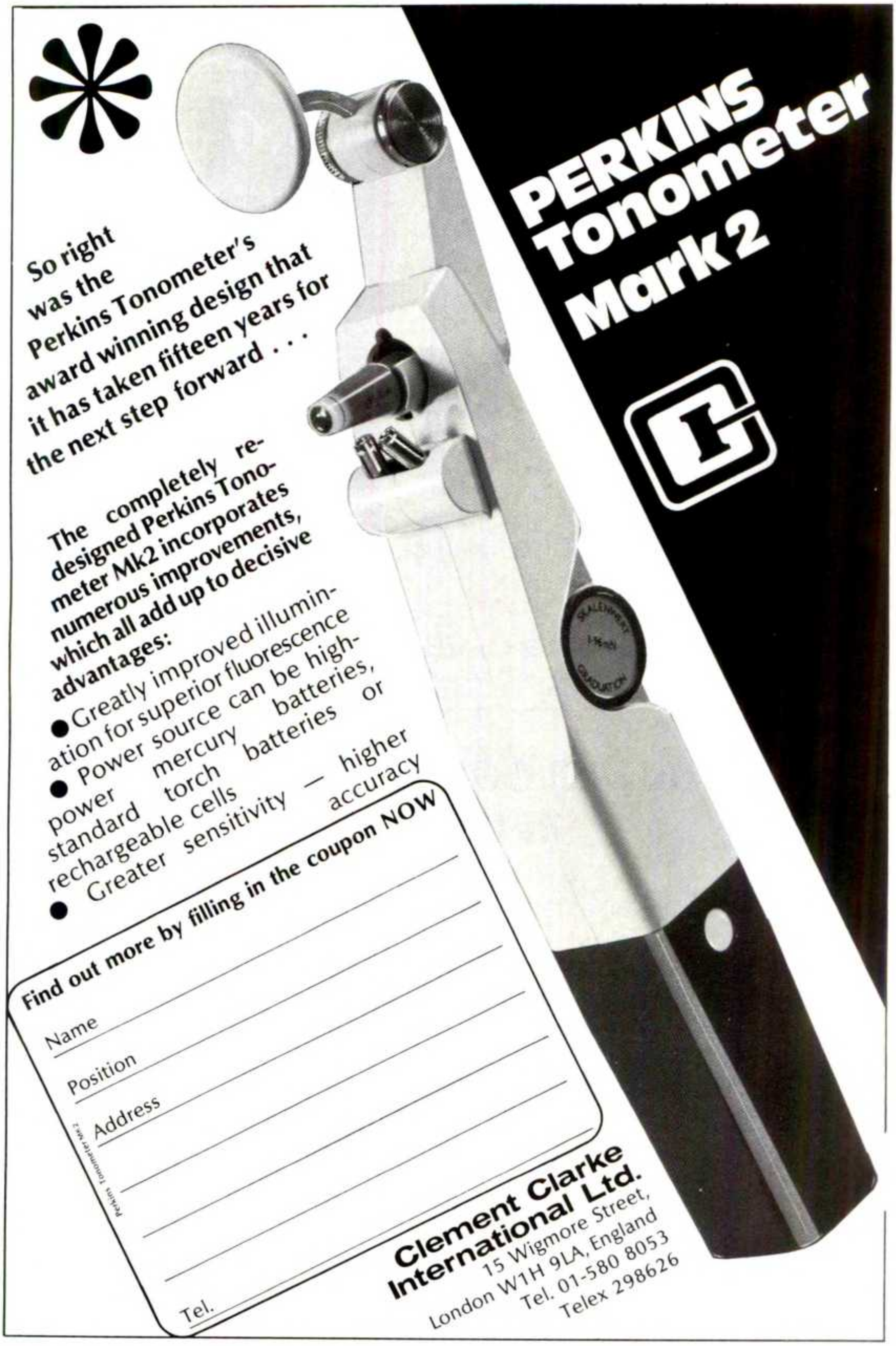

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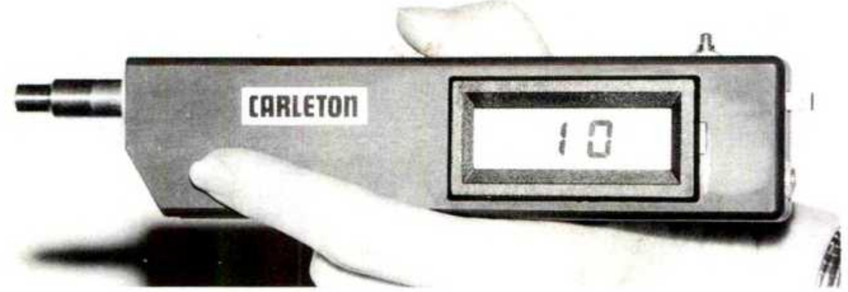

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Editorial: In honour of Professor Barrie Jones

In 1951 there arrived in London a young New Zealand ophthalmologist seeking further postgraduate training who was destined to become one of a select band of his countrymen who have made unique contributions to British and world medicine. Subsequently in 1963 Barrie Jones was appointed to head the newly inaugurated Department of Clinical Ophthalmology of the Institute of Ophthalmology and Moorfields Eye Hospital. Incidentally he was the first holder of an established chair in clinical ophthalmology in any English university. Under his leadership the department soon became renowned as a centre for research and teaching and attracted many young academic ophthalmologists and scientists from Britain and overseas.

In 1981 he resigned from the chair of clinical ophthalmology to establish and lead a new Department of Preventive Ophthalmology at the Institute. He was thereby enabled to devote his talents and energy to the problem of world blindness, a matter which had been close to his heart for many years. The time was right for this development and he was uniquely equipped to spearhead the challenge against one of the most pressing human problems of the age.

All too soon Barrie Jones is to retire from the Institute and Moorfields, and it is this event which the *BJO* is marking by dedicating this number as a Festschrift in his honour. The contributors have been members of his departments or closely associated with his work in other ways; all are colleagues and friends who are proud to have sat at his feet. The *BJO* salutes an outstanding ophthalmic physician and surgeon, an innovative and visionary scientist, and above all a great doctor. We know that his 'retirement' will be very active and we send him and his devoted wife, Pauline, affectionate good wishes for the future.

NSCR

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Ocular findings in a double-blind study of ivermectin versus diethylcarbamazine versus placebo in the treatment of onchocerciasis

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SUMMARY The effect of ivermectin, a new microfilaricide, was assessed in a double blind trial against diethylcarbamazine citrate (DEC) and placebo. Fifty-nine adult males with moderate to heavy infection with *Onchocerca volvulus* and with eye involvement were recruited from an area under Onchocerciasis Control Programme (OCP) vector control in Northern Ghana. They were randomly assigned to an eight-day treatment with ivermectin as a single dose of 12 mg on day 1 followed by placebo for the remaining seven days, or DEC, total dose 1·3 g, or placebo, and ophthalmological review was undertaken over a period of one year. DEC acted quickly to eliminate microflariae from the eye and was associated with reactive ocular changes and in a few cases functional deficit. Ivermectin eliminated microfilariae slowly from the anterior chamber of the eye over a period of six months. The ocular inflammatory reaction was minimal and no functional deficit occurred. It is postulated that the observed slow action of ivermectin on the eye may be attributed in part to its inability to cross the blood-aqueous humour barrier because of its molecular size as a macrocyclic lactone causing microfilariae to leave the eye gradually along a newly created gradient. Ivermectin is an effective microfilaricide with minimal ocular adverse effect and could therefore be suitable for widespread application without strict supervision.

Diethylcarbamazine (DEC)[1-6] and suramin[5-11] have been used for over three decades in the treatment of ocular onchocerciasis. When used judiciously under steroid cover, DEC may cause lesions of the anterior segment of the eye to resolve,[12-14] but no such advantage is thought to occur in respect of posterior segment ocular involvement.[5 12 15 16] Recently it has been shown by fluorescein angiography[17] that new or increased retinal pigment epithelial and optic nerve disease can occur during treatment of ocular onchocerciasis with DEC and that such disease is associated with functional loss. The eye damage appears to be an exaggerated form of the inflammatory reaction that occurs under natural conditions. These ocular complications as well as other systemic side effects of therapy have discouraged indiscriminate mass treatment with DEC, and its unrestricted use is not recommended.[18] There is therefore a need for a safer drug for the treatment of onchocerciasis.

Ivermectin, a macrocyclic lactone, was first reported in 1982[19] to be effective in the treatment of patients lightly infected with onchocerciasis and to cause little or no Mazzotti reaction, a generalised inflammatory reaction following DEC therapy in response to microfilarial death. The efficacy was confirmed in subsequent studies,[20-22] which also reported ivermectin to be safe to the eye. Recent reports on double blind comparative studies of ivermectin, DEC, and placebo[23 24] have also supported these conclusions.

Correspondence to Dr K Y Dadzie.

This paper reports on further experience with ivermectin in the treatment of ocular onchocerciasis in a double blind study comparing ivermectin, DEC, and placebo in an area subject to vector control under the WHO Onchocerciasis Control Programme (OCP).

Patients and methods

PATIENT SELECTION

Fifty-nine otherwise healthy adult males aged between 15 and 50 years with moderate to heavy infection with *Onchocerca volvulus* and with eye involvement were recruited from 10 villages in the savannah area of northern Ghana where vector control has interrupted the transmission of infection since 1976. All patients were admitted to hospital at the Onchocerciasis Chemotherapeutic Research Centre (OCRC), Tamale Hospital, during drug administration and for several days afterwards. They were readmitted for one or two days for each subsequent examination.

Forty-eight of the 59 patients were retained for ophthalmological analysis. Of the 11 excluded, seven were absent for one of the three- or six-month follow-up examinations (three who received DEC, three ivermectin, and one placebo), and a further four absconded after the second day of treatment (two in the ivermectin group and two in the placebo group). One patient who took DEC and who was absent at day 28 was retained; his microfilarial counts on day 28 were estimated as the mean between those found at day 14 and at three months. Of the 48 patients retained, 17 received DEC, 15 ivermectin, and 16 placebo.

METHODS

General examination. A detailed systemic examination was carried out. Values for the parameters used in the quantitation of the Mazzotti reaction[25] were collected. Haematological and biochemical tests were done as well as routine examination of urine and the examination of membrane filtered urine and blood for microfilariae. These examinations were conducted before treatment started, during the first 10 days of treatment, and at subsequent follow-up visits. Skin snips were taken with a Walser corneoscleral punch from the left outer canthus and from both scapulae, iliac crests, and calves. The microfilarial density for each patient was expressed per mg of skin using the mean of the counts from the four sites on the left. Skin snips were repeated on days 2, 4, 8, 14, and 28 and at 3, 6, 9 and 12 months after the start of treatment. Nodulectomy was carried out at one and six months to determine the effect of the drug on the adult worm.

Ophthalmological examination. This was undertaken before treatment began and on the 2nd, 4th, 8th, 14th, and 28th days and 3, 6, and 12 months after the start of treatment. This included a visual acuity test using the illiterate E chart at 6 m distance for each eye separately and without correction for refractive error as well as a visual field test using 1 m Bjerrum tangent screen with a 2 mm white target in daylight at 1 metre distance. Slit-lamp examination was conducted after head down positioning of patients for at least two minutes to facilitate and standardise counting of microfilariae in the anterior chamber. Microfilariae, both dead and alive, and onchocercal punctate keratitis in the cornea were counted. The intraocular pressure was measured after the examination of the anterior segment of the eye was completed. The fundus was examined by both direct and indirect ophthalmoscopy after pupil dilatation. Fundus photography and fluorescein angiography were undertaken with a Topcon TRC fundus camera initially and later a Kowa RC2.

Drug administration. Twenty patients received DEC in a dose of 50 mg each morning for two days and then 100 mg twice daily for a further six days; 20 received ivermectin in a single dose of 12 mg on the morning of the first day and placebo capsules thereafter; and 19 received matching placebo capsules containing 185 mg corn starch (STA-RX L500) per capsule for the duration of therapy. The drugs, which were formulated in identical capsules and precoded, were allocated randomly to patients on arrival in the hospital. An elaborate check system was conducted to ensure correct drug administration and complete ingestion.

Statistical analysis. Non-parametric significance tests have been applied. The Kruskal-Wallis one-way ANOVA was used to compare all three treatment groups and the Mann-Whitney U test to compare the two treatment groups on each examination day. Within each group the post-treatment data were compared with baseline data by the Wilcoxon matched pairs, signed-ranks test. The study code was broken after the six months follow-up examination.

Table 1 *Pretreatment general features of patients in the three treatment groups*

Feature	*Treatment group*		
	DEC (*n*=*17*)	*Invermectin* (*n*=*15*)	*Placebo* (*n*=*16*)
Age	33 (18–45)	32·1 (17–50)	30·1 (15–47)
Weight (kg)	56·7 (44–65)	57·0 (42–67)	55·3 (46–69·6)
Skin atrophy*	9	8	4
Nodules*	16	14	13

*Number of cases with the onchocercal lesion.

Table 2 *Important pretreatment ocular lesions and changes occurring after treatment*

	Pretreatment ocular status								*New lesions*		
	Visual acuity			*Visual field defect*	*Ophthalmoscopy/ fundus photo*		*Fluorescein angiogrphy*		*Field loss*	*Disc leak*	*RPE abnormality*
	A	*B*	*C*		*Disc lesions*	*Retinal lesions*	*Disc leak*	*RPE abnormality*			
DEC citrate (n=17)	13	3	1	10	11	8	13	8	2	2	4
Ivermectin (n=15)	13	2	0	8	7	8	10	5	0	2	2
Placebo (n=16)	13	0	3	8	9	4	13	8	0	0	2

Figures indicate number of cases.
Visual acuity of worst eye: A=6/4–6/9. B=6/12–6/24. C=≥6/36.
RPE=retinal pigment epithelium.

Results

PRETREATMENT

General. The patients in the three treatment groups were similar with regard to age, weight, symptomatology, and systemic clinical findings (Table 1). The means of the skin microfilarial counts with 95% confidence limits in patients treated with DEC, ivermectin, and placebo were 112 (81–154), 154 (107–223), and 138 (104–184) respectively.

Ocular

Visual function. The visual acuity in all but nine patients was 6/9 or better with each eye. The reduced visual acuities were not attributed to onchocerciasis in any patient.

More than half the patients had abnormalities of visual fields which were predominantly constriction or arcuate defects resulting from onchocercal optic nerve disease, or corresponded to choroidoretinal disease. The frequency of occurrence of normal and abnormal visual acuity or peripheral visual fields was similar in the three treatment groups (Table 2).

Ocular parasites. Forty-four of 48 patients, 15 in the DEC group, 14 in the ivermectin group, and 15 in the placebo group, had ocular microfilariae. Microfilariae were found predominantly in the anterior chamber of the eye. Patients who took DEC tended to have lowest counts (Fig. 1), but there was no statistically significant difference between the three treatment groups (p=0·16, Kruskal-Wallis test). Microfilariae were found in small numbers (fewer than 10) in the corneae of 11 patients—two in the DEC, six in the ivermectin, and three in the placebo group. Punctuate keratitis occurred in two patients each in the DEC and ivermectin groups. There were no statistically significant differences among the three groups.

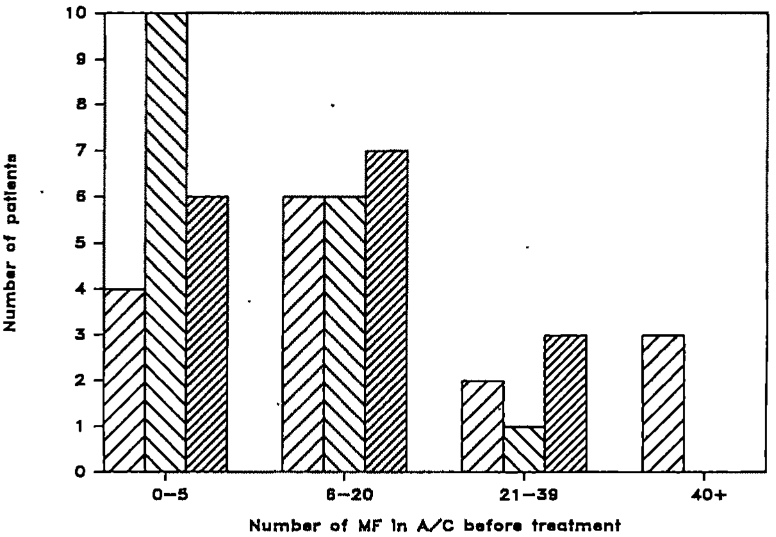

Fig. 1 *Pretreatment distribution of microfilariae in the anterior chamber of the eyes in patients treated with ivermectin, DEC, or placebo.* ▨ *=ivermectin (n=15).* ▧ *=DEC (n=17).* ▩ *= placebo (n=16). MF= microfilariae. A/C=anterior chamber.*

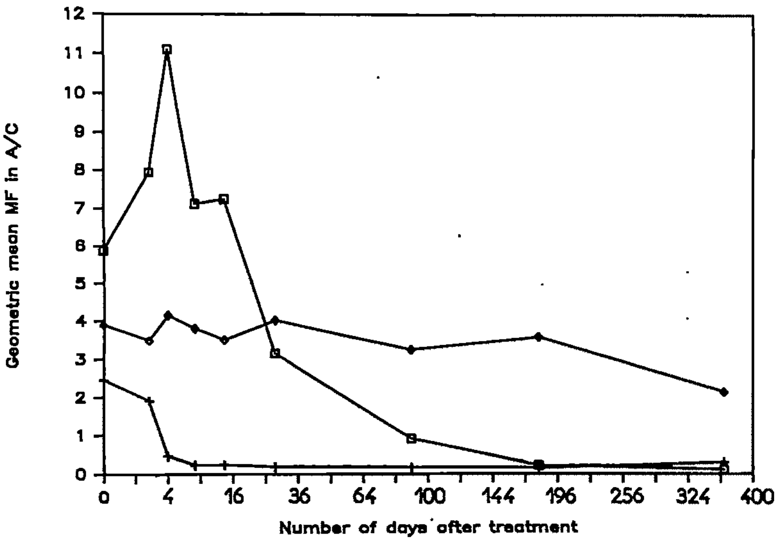

Fig. 2 *Changes in the microfilarial load in the anterior chamber of the eyes in patients treated with ivermectin, DEC, or placebo.* □——□=*Ivermectin (n=15).* +——+=*DEC (n=17).* ◊——◊= *Placebo (n=16).*

Ocular fundus. Nearly 60% of the patients had onchocercal fundus lesions (Table 2). Mild atrophy of the temporal retinal pigment epithelium was found frequently, but occasional severe forms extended nasally towards the optic disc. Severe choroidoretinal scarring was found in one patient each in the DEC and ivermectin groups. Chronic low grade optic neuritis, frank as well as in the early stage of optic atrophy, was found at about the same frequency in each group. With fluorescein angiography still earlier grades of these fundus lesions were detected. These were distributed in a similar frequency among the treatment groups.

RESPONSE TO TREATMENT

General

Systemic reactions. Headache, joint pains, muscle aches, and cardiovascular reactions were found with equal overall severity in both treatment groups. However, itching, node pain and tenderness, tachypnoea, and rash were more severe in DEC than in ivermectin treated patients. Fever was more prominent with ivermectin treatment than with DEC. Acute febrile polyarthritis involving the knees, ankles, elbows, and small joints of the hands and feet, which occurs classically several days after initiation of therapy, was observed in five patients treated with DEC but in none of those treated with ivermectin.

Skin microfilariae. Both DEC and ivermectin treated groups showed a similarly significant decrease in the mean microfilarial density compared with the placebo treated group, with the lowest mean level of 1·3 microfilariae per mg of skin at day 8 for DEC and 0·9 at day 14 and 28 for ivermectin. Both groups showed a slight rise at six months, but at 9 and 12 months the DEC treated group had reached a significantly higher level than the ivermectin group.

Adult worm. No macrofilaricidal effect was observed on adult worms removed at both one and six months with either DEC or ivermectin. A remarkably high number of degenerate microfilariae were seen in gravid worms taken at six months from patients treated with ivermectin.

Ocular

Changes in ocular parasite load. DEC caused rapid elimination of microfilariae from the anterior chamber, reaching near zero level by day 8, and remaining at this level with only minor fluctuation over the period of one year (Fig. 2). This reduction, compared with that in the placebo treated group, is

Table 3 *Statistical significance of observed differences between treatment groups in microfilarial counts in the anterior chamber (Mann-Whitney U test)*

Day of treatment	*Day 0*	*Day 2*	*Day 4*	*Day 8*	*Day 14*	*Day 28*	*Month 3*	*Month 6*	*Month 12*
DEC vs ivermectin	NS	<0·05	<0·001	<0·001	<0·001	<0·001	NS	NS	NS
DEC vs placebo	NS	NS	<0·001	<0·001	<0·001	<0·001	<0·001	<0·001	<0·01
Ivermectin vs placebo	NS	NS	<0·05	NS	NS	NS	<0·05	<0·001	<0·001

NS=p>0·05.

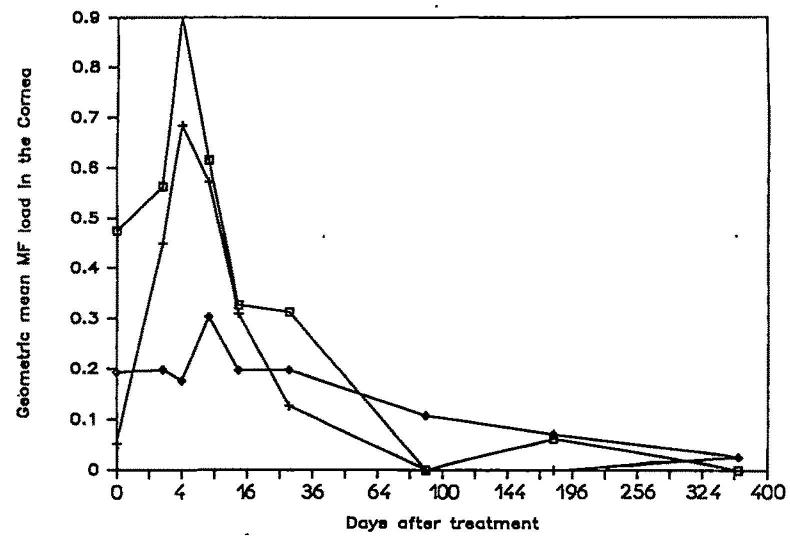

Fig. 3 *Changes in the corneal microfilarial load in patients treated with ivermectin, DEC, or placebo. □——□=Ivermectin (n=15). +——+=DEC (n=17). ◊——◊= Placebo (n=16).*

significant from day 4 onwards (Table 3). With ivermectin a significant increase of the microfilarial load from the pretreatment level occurred, with a peak at day 4 ($p<0.001$, Wilcoxon signed-ranks test), followed by a gradual decrease to significantly lower than that for placebo at three months and to near zero level (similar to DEC) by six months. The placebo treated group showed no rapid change in the microfilarial load, though at one year it appeared reduced.

Both the DEC and ivermectin groups increased from the baseline corneal microfilarial count to a peak on day 4; the increase caused by DEC was significant on days 2, 4, and 8 ($p<0.01$) (Fig. 3). Compared with placebo, both DEC and ivermectin increased the corneal microfilarial load significantly on day 4 ($p<0.05$). Increase in onchoceral punctate keratitis occurred mainly with DEC and was significant on days 4 ($p<0.01$), 8 ($p<0.01$), and 14 ($p<0.05$) (Wilcoxon signed-ranks test), but was significantly increased compared with placebo only on day 4 ($p<0.01$; Mann-Whitney U test.

Inflammatory signs. Mild or moderate limbitis occurred more frequently in the DEC group than in the ivermectin group; a moderate limbitis was observed in one patient only who took ivermectin. (Table 4). An increase in fluffy corneal opacities was seen only in patients treated with DEC (Fig. 4). In the placebo group only occasional limbal injection was observed. Mild flare was observed at a similar frequency in both the DEC and ivermectin groups and less frequently in the placebo group. One case of mild to moderate iridocyclitis occurred in each of the ivermectin and placebo groups but none in the DEC group.

Fundus changes. Four patients with optic disc changes were observed with fluorescein angiography, of whom two had received DEC treatment. One of these showed increasing disc hyperfluorescence from day 2 to 28 and fresh pigment epithelial lesions.[17] This patient lost fields bilaterally and progressively from day 4, to stabilise as bilateral contracted fields by day 14. The other patient showed an increasing disc hyperfluorescence from day 2 to 8 without pigment epithelial change but with accompanying left eye field loss on day 2, followed by the right on day 4, and progressing gradually until day 28. The two other

Table 4 *Comparison of inflammatory signs*

Days of treatment	*DEC (n=17)*							*Ivermectin (n=15)*							*Placebo (n=16)*						
	2	*4*	*8*	*14*	*28*	*90*	*180*	*2*	*4*	*8*	*14*	*28*	*90*	*180*	*2*	*4*	*8*	*14*	*28*	*90*	*180*
Limbal injection	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	2	0	0	0	0
Limbitis: mild	7	8	4	0	0	0	0	3	0	1	0	0	0	0	0	0	0	0	0	0	0
moderate	3	4	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Flare	3	3	0	1	2	1	0	4	2	0	0	1	0	0	0	1	1	1	0	0	0
Iridocyclitis: mild	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0	1	1
moderate	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0

NB: No inflammatory sign was observed at 1 year follow-up.

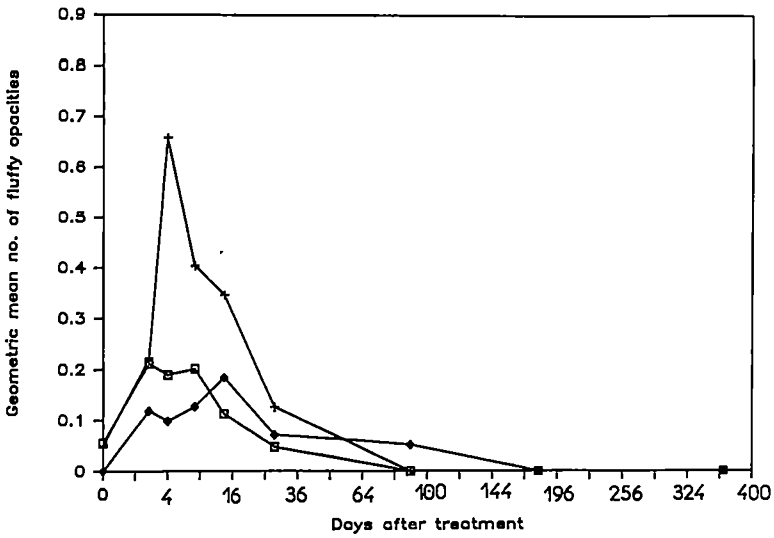

Fig. 4 *Changes in the punctate keratitis (fluffy opacities) load in patients treated with ivermectin, DEC, or placebo. □——□= Ivermectin (n=15). +——+=DEC (n=17). ◊——◊=Placebo (n=16).*

patients who had received ivermectin showed increased disc hyperfluorescence from day 2 to 28; however, there was no associated visual functional deficit. Optic disc hyperfluorescence that existed initially in six patients who took DEC, seven who took ivermectin, and three who took placebo resolved by one year. New minor pigment epithelial changes were visible at the one-year follow-up in four patients who received DEC, two who took ivermectin, and two who received placebo.

Other ocular changes. Changes in intraocular pressures in the course of the study did not show any definite pattern. No significant changes in the visual acuities were encountered. No other pathological changes were observed in the course of the study.

Discussion

The effect of a microfilaricide may be observed and quantified by observing the death or the elimination of microfilariae from the anterior segment of the eye and the tissue reaction to dead microfilariae.

In this study the evidence for the elimination of microfilariae from the anterior segment of the eye by both DEC and ivermectin is demonstrated. Despite the low counts of corneal microfilariae initially, which is a normal finding in patients in an area under vector control,[26] the mobilisation of microfilariae into the cornea[12] during the first week of treatment occurred in both the DEC and ivermectin treated groups, the effect with DEC being the greater. However, only DEC caused a significant increase in onchocercal punctate keratitis. This phenomenon has also been observed in similar trials.[22 23] As in our previous open study,[22] the most striking finding was the mobilisation of microfilariae into the anterior chamber by ivermectin to a peak on day 4 which was a significant increase from baseline, followed by elimination to zero level by six months, while DEC promptly eliminated microfilariae to near zero level by day 8.

Although it is believed that the antiparasitic effect of ivermectin may result from its action in the mediation of neurotransmission by γ-aminobutyric acid,[27] and although ivermectin has been shown to kill *Onchocera lienalis* in vitro,[28] the precise mode of action of ivermectin in human ocular onchocerciasis is unknown, and several factors may have a contributory role. As a macrocyclic lactone, it is possible that ivermectin cannot cross the blood-aqueous humour barrier to enter the anterior chamber of the eye and exert direct action on the microfilariae. Ivermectin may conceivably act by eliminating the source of microfilariae migrating into the eye from surrounding skin and orbital tissue, thus reversing the microfilarial concentration gradient. Microfilariae may then leave the anterior chamber along this gradient, possibly along the same route by which they entered, or they might die naturally. This lack of microfilaricidal effect of ivermectin in the eye might account for the paucity of ocular inflammatory reaction. By contrast, DEC has been shown to enter the anterior chamber of the eye in therapeutic concentrations.[29] However, it is believed that DEC does not cause microfilarial death directly, but causes dissolution of the outer protective layer, which is followed by killing of the microfilaria by cellular immune mechanisms. Thus DEC causes death of microfilariae only in vivo but not in vitro. It has been suggested that in the anterior chamber of the eye, where cellular defence mechanisms are absent, DEC can only unmask microfilariae. This led to the suggestion that DEC in therapeutic doses mobilises vulnerable microfilariae from the anterior chamber either into ocular tissues or out of the eye where they are killed.[30, 31] It is well recognised that one of the properties of DEC is the mobilisation of microfilariae.[12]

The postulated actions of the two drugs may explain the difference in time taken to eliminate microfilariae from the anterior chamber of the eye as well as differences in ocular tissue reaction in the form of inflammation. Limbitis, which can be used to quantify the severity of host reaction to a microfilaricide,[32] occurred in the majority of patients treated with DEC but rarely in those treated with ivermectin. DEC caused optic nerve and pigment epithelial changes with functional deficit; although ivermectin caused papillitis, this was mild and was not associated with any defect in function. In similar studies[23, 24] no changes at the posterior segment of the eye were observed in ivermectin treated patients.

Although the incidence of eye changes associated with DEC treatment in this study is quite considerable, it is still less than that reported by Bird *et al.*[17] in their study of 21 patients who were observed for two weeks in southern Sudan. Factors that may contribute to this difference may be: (1) the intensity of infection of the patients, which is lower in this study; (2) possible differences in the pattern of disease in the two different subregions; and (3) the possibility of changing host reaction in association with the interruption of transmission of infection. The absence of transmission of infection has been shown to lead to a decrease in the microfilarial load in the eye,[26] and this is reflected in the decreased microfilarial load of the anterior chambers and the resolution of papillitis in the placebo group after one year, as diagnosed by fluorescein angiography.

This double blind study in patients living in an area subject to OCP vector control shows that ivermectin exerts a slow microfilaricidal effect on the eye, but, unlike DEC, does not produce any serious inflammatory reaction likely to cause functional deficit. These observations accord with those of our previous study.[22] In the light of similar conclusions drawn from studies undertaken where transmission of *O. volvulus* continues unabated[23, 24] it would appear that treatment with ivermectin is not associated with serious ophthalmological adverse effect and may be suitable for mass treatment. Further studies in patients with very heavy ocular infection are clearly needed.

We are grateful to Merck Sharp and Dohme Research Laboratories for the supply of ivermectin and for financial support, to Dr Samba, Programme Director, Onchocerciasis Control Programme, for his keen interest in and support for the study and to J Remme for his invaluable statistical advice and support.

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Perinuclear lens retrodots: a role for ascorbate in cataractogenesis

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SUMMARY Lens retrodots are round, oblong, or oval features in the perinuclear zone of the adult lens after the fifth decade of life and associated with cataract. Retrodots were found in 47 out of 121 eyes with cataract (39%) in the present series. They show birefringence in vivo and in vitro, and chemical studies suggest that they contain calcium oxalate. It is proposed that ascorbic acid, which is abundant in the normal human lens, is the most likely source for this oxalate. Ascorbic acid is thought to have a protective role against oxidative stress in the lens and other parts of the eye, and its level is known to be reduced in senile cataract. The presence of the retrodots may identify lenses which have been exposed to oxidative stress and are less capable of resisting oxidative damage.

Vogt described a feature seen in the adult lens by specular microscopy with the slit-lamp.[1,2] He observed a 'relief pattern' of knobs and bumps softly delineated from the adjacent cortex and distributed over the anterior perinuclear surface. With Lussi he prepared accurate models of these changes.[3] Reese and Wadsworth,[4] unaware of these studies, reported a change found in the anterior and posterior surfaces of the adult lens which they termed 'cystoid spaces', stating them to be present in 10% of otherwise normal lenses, though they did not define their population. A further report by Bron and Matsuda[5] and a more detailed paper by Bron and Brown[6] termed these changes 'retrodot' lens opacities because of their ease of visibility against the red reflex in contrast to their poor visibility by focal slit-lamp illumination. They emphasised that the features are seen by both retro and specular modes of illumination. All authors are agreed that the isolated changes have only a small effect on vision.

In this paper these features are discussed in detail and an attempt is made to relate them to certain other chemically characterised lens opacities.

Definitions of lens zones

The literature abounds in different definitions of the zones of the lens. This often leads to descriptive confusion. The definition used here is as follows.[6] The lens consists of nucleus and cortex (Fig. 1).

NUCLEUS

The 'nucleus' in this paper will be taken to be that portion of the central lens (e.g., in the adult) which represents the lens at birth. Since the lens at birth has a diameter of approximately 6·0 mm, this is the size of the lens nucleus as defined here. It is implicit in this terminology that all lens fibres added after birth will be designated *'cortex'*. This approach avoids the

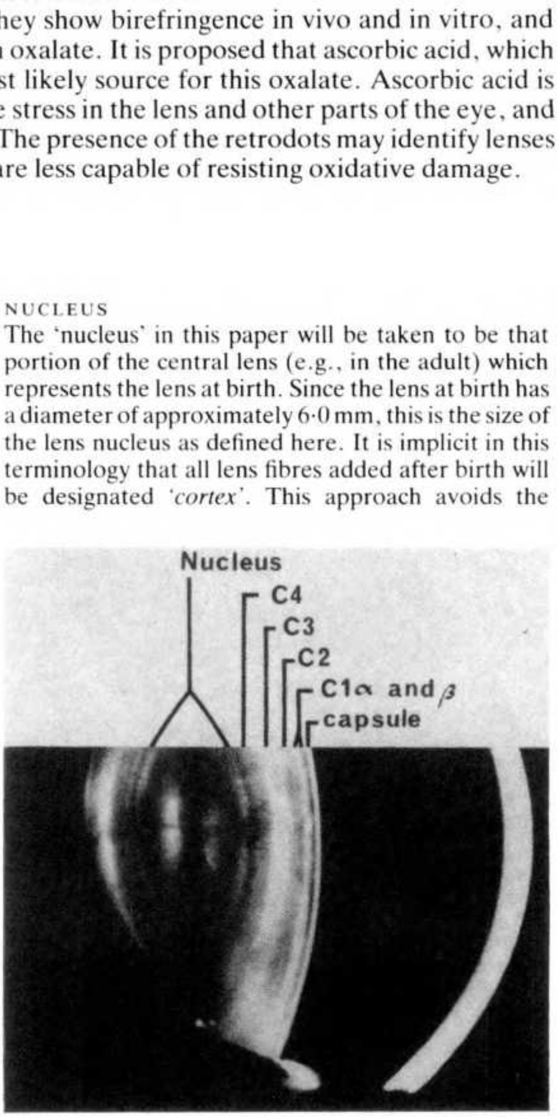

Fig. 1 *Classification of the zones of the adult lens.*

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confusion which arises from such terms as 'infantile nucleus', representing the size of the lens at some time in infancy. Clearly such an approach results in the same part of the lens being referred to as cortex in youth and nucleus in later life.

The lens nucleus as described here is well demarcated optically from subsequent cortical layers and is that part of the lens which in later life first develops the colouring and scattering changes commonly referred to as nuclear sclerosis. This approach therefore has both descriptive value and probably biological significance.

CORTEX

In the young adult lens the cortex displays four optically distinct layers in the slit beam. These layers are retained throughout life, though they become subdivided by the acquisition of further optical zones of discontinuity.

The outer two zones (C1 and C2) are designated superficial cortex, while the inner two (C3 and C4) are termed the deep or perinuclear cortex. (Zone C1 includes a clear zone $C1_\alpha$, and the first bright band or zone of disjunction which is designated $C1_\beta$). Perinuclear cortex has the distinction of being strongly autofluorescent, emitting a bright apple green fluorescence when stimulated with blue light.[7] This autofluorescence falls off abruptly to either side of C3 and C4 (that is, it is less marked in the nucleus and in C1 and C2). Autofluorescence may be appreciated by means of the standard blue exciting source of the slit-lamp—for example, combined with a Kodak Wratten No. 15 yellow barrier filter.

Methods of examination

Focal illumination uses a broad slit beam and examines the scattering properties of the lens. The common focal dot opacities of the lens are best seen in focal illumination.

Slit examination employs a narrow beam and examines the lens in optical section.

Red reflex examination. (*a*) Conventional retroillumination directs a broad vertical beam through the pupil at one side and provides indirect retroillumination. (*b*) The Fincham-Kawara system employs for example a Zeiss Photo-Slit Lamp whose optical head has been removed. Light is directed centrally through the pupil by a 45° glass plate, the incident beam passing through a polarising filter. The reflected beam passes through a further polarising filter at right angles to the first. This arrangement blocks out the corneal reflection but, since light returning from the fundus is no longer polarised the red reflex may be viewed though the luminosity is reduced.[8 9] A modified system is used here.

Specular microscopy. Changes in contour are observed when light is reflected from a refractive interface.

Features of lens retrodots

DEFINITION

Lens retrodots are small, discrete, smooth contoured features located anteriorly and posteriorly in cortical zones C3 and C4. They are seen well by retroillumination and specular microscopy and less well by focal illumination.

SHAPE AND SIZE

Retrodots seen against the red reflex are round, oblong, or oval or sometimes have a lobular appearance suggesting coalescence of adjacent lesions, or superimposition of opacities lying at different depths (Figs. 2, 3). Probably both forms occur. Their contours are always smooth. They vary in apparent size from 80 µm to 500 µm with a modal value of about 300 µm (measured on red reflex photographs without correction for magnification). The anterior retrodots are more easily seen than the posterior retrodots, a point also noted by Reese and Wadsworth.[4]

DISTRIBUTION AND LOCALISATION

It may be easily seen in the red reflex that the retrodots are disposed in a circular or somewhat spiral manner, concentric with the anteroposterior axis of the lens and suggesting a relationship to the fibre arrangement (Figs. 2, 3). The long axis of the oval retrodots is often also concentric in the same way. The dots are located at varying depths in a continuous anterior and posterior shell of cortex at the level of C_3 and C_4 and may also be observed in the superficial layers of the nucleus. The lens may show one or two, or there may be a crowded field of retrodots in roughly the same plane. In one patient, aged 71 years, 400 were counted in a single lens in the anterior perinuclear cortex. Peripheral dots are often smaller than central dots. Small peripheral dots may sometimes be seen so far peripherally that it is likely they reside outside perinuclear cortex and therefore in C_2.

OPTICAL FEATURES

Retroillumination (Figs. 2, 3, 4)

In the red reflex the dots may be clear in content, and, if the light source is offset with conventional, indirect retroillumination, the pattern of luminosity is reversed, that is, the dots exhibit a light and a dark zone, with the light zone on the *opposite* side to the retinal illumination. This is in contrast with the pattern created by lens vacuoles, which is unreversed

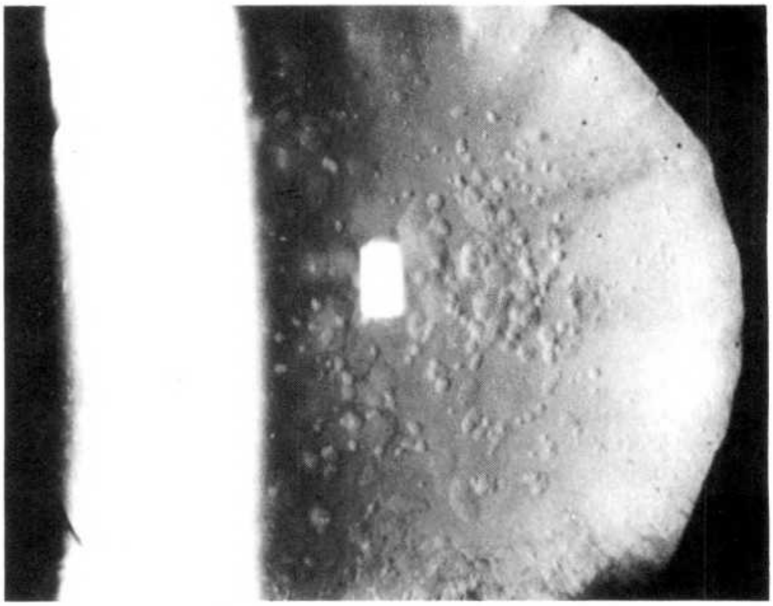

Fig. 2 *Multiple retrodots in a 71-year-old lens by indirect retroillumination.*

(that is, with the light field on the same side as the illumination source). The unreversed pattern is thought to be generated by an optical medium of lower refractive index than its surrounding, while the reversed pattern is generated by a medium of higher refractive index.[10] At times the dots may appear slightly opaque and granular. Sometimes they have a tiny dark dot within the substance, seen against the red reflex. At other times, when the illumination source is angled to give a relatively dark red reflex, the retrodots may appear bright and relatively opaque (Fig. 4a). This probably occurs when the structures are illuminated more obliquely.

If the lens is viewed with crossed polarisers, the retrodots are either less visible than when viewed

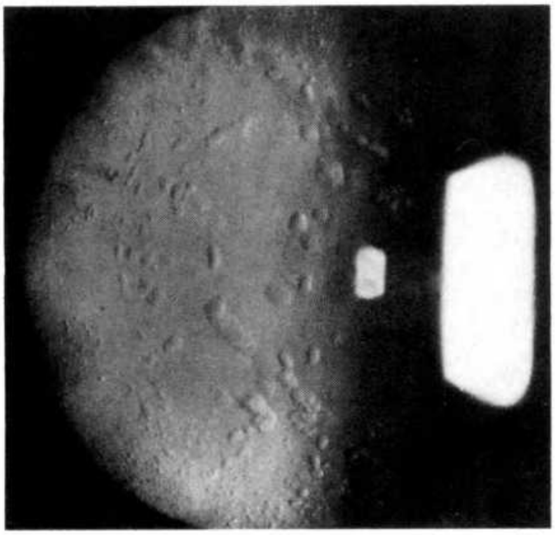

Fig. 3 *A less obvious example of retrodots in a 69-year-old lens. These are easily overlooked unless a careful search is made with indirect retroillumination.*

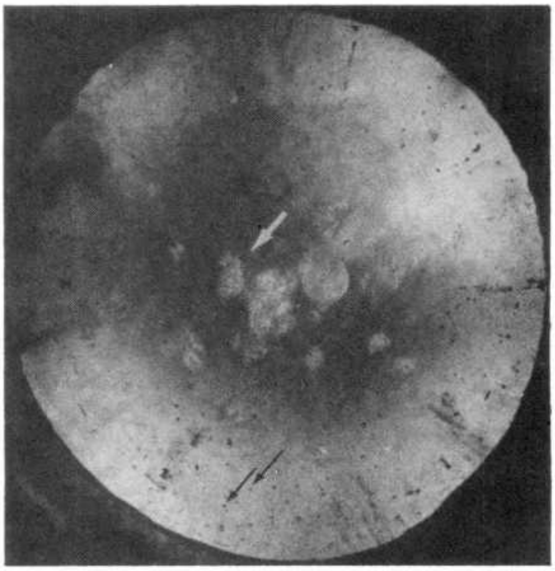

Fig. 4a *Retrodot lens opacities showing a bright crystalline birefringent structure by retroillumination in polarised light (same eye as in Fig. 2). Focal dot opacities are seen in the periphery of this lens as dark silhouettes. (The perfectly round light is an artefact.) Patient aged 81.*

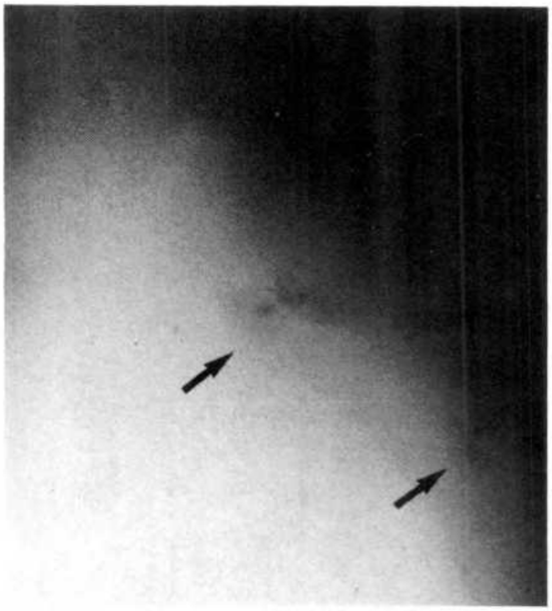

Fig. 4b *Retrodots appearing as dark 'butterflies' in polarised light in the presence of nuclear slcerosis. Retrodots arrowed.*

by the conventional mode or they show a highly luminous profile, appearing as bright points of whitish light, often with a punctate pattern, against the red reflex. This appearance suggests that they exhibit birefringence and are visible by reflection and rotation of the ingredient polarised light. In some circumstances, in the presence of a scattering nucleus, they appear as dark 'butterflies' on a light ground (4b).

Slit illumination

Retrodots are not always visible by slit illumination. However, they may be visible as narrow crescentic or narrow oval slits most readily demonstrated when they occur in association with nuclear sclerosis. Then they are seen as clear, dark, 'cystoid' spaces against a coloured and highly scattering ground. These cystoid spaces are usually at the level of C_3 and C_4 anteriorly and posteriorly, but may also be found occasionally in the superficial nucleus (Figs. 5 and 6).

Focal illumination

In focal light the retrodots are invisible, or faintly visible as an opalescent structure. This scattering is never marked. Occasionally, when the retrodots are associated with a marked nuclear scattering, a single polarising filter placed in the incident beam will render the dots visible as a dark granular opacity seen against the bright scattering ground; with rotation of the polariser the opacities may then be made to disappear (Fig. 7).

Specular illumination

The anterior retrodots are visible by specular microscopy as elevations convex forwards (Fig. 7). Their visibility is enhanced with increasing age, when so-called lamellar separation of the cortical layers increases the specular features of the anterior cortex. The margins of the retrodots are less well defined by

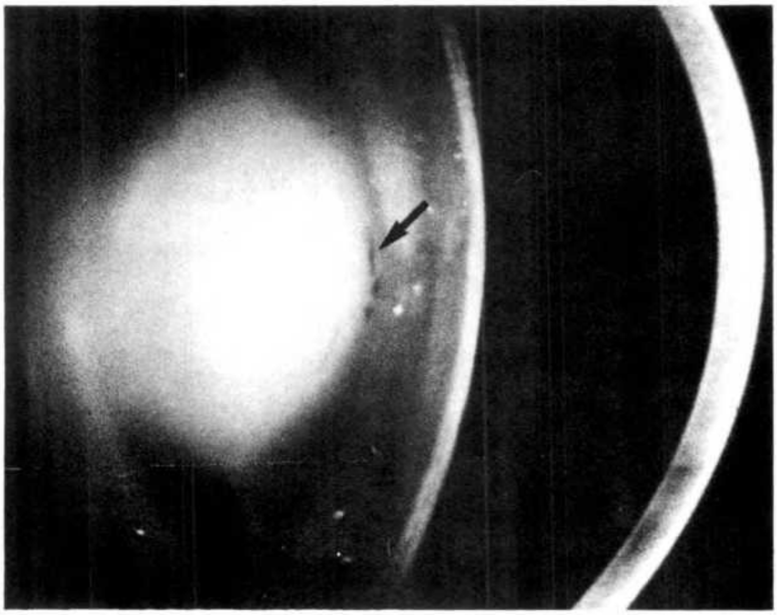

Fig. 5 *A slit image picture in which the presence of retrodot opacities is shown by clear clefts in the anterior perinuclear region of the lens cortex (arrowed). This lens also shows marked nuclear sclerosis.*

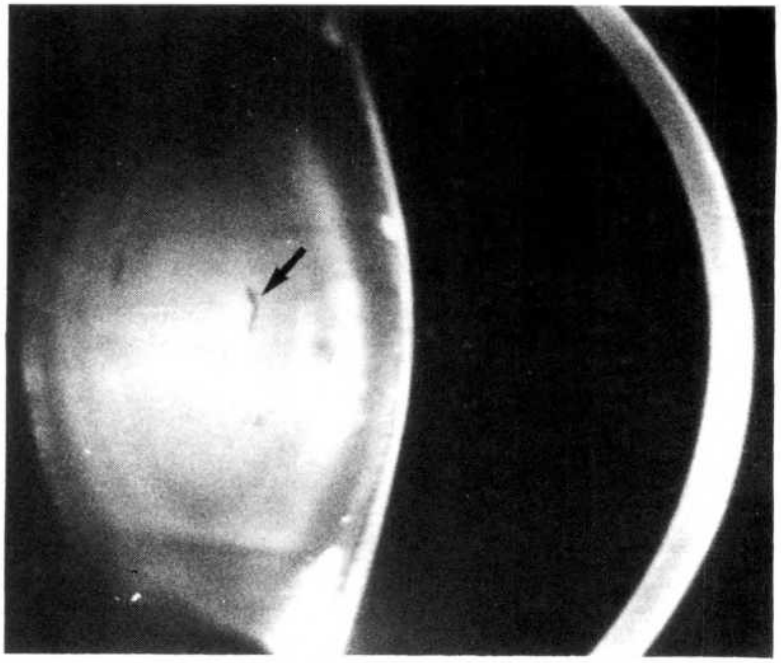

Fig. 6 *Slit image picture of a 71-year-old lens showing retrodots in the perinuclear cortex and also clefts within the nucleus, which are presumed to represent more deeply situated retrodots.*

specular microscopy than in the red reflex. Posterior retrodots are not seen by specular microscopy.

With the various modes of illumination discussed the impression is created of a discoid structure lying in the perinuclear cortex, flattened in the plane of adjacent layers of lens fibres, and whose superficial surface is convex towards the surface of the lens.

ASSOCIATED LENS CHANGES

In 73 clinic and ward patients with cataract (aged 35–93 years) retrodots were observed in 47 out of 121 eyes (39%). As the sample is non-random, no special conclusions can be drawn from this association other than that retrodot changes are common, but a population study is in progress and the relationship between retrodot changes and other cataractous changes is being studied.

VISION

When lens retrodots occur in isolation or in small numbers, they have no effect on vision. In larger numbers they may cause a more definite reduction to the 6/9 region. When they are associated with nuclear sclerosis it appears that visual function may be more seriously affected than when either occurs alone.

ONSET AND PROGRESSION

Retrodots appear to be acquired in the 40s, in the presbyopic period. It is likely that they increase in number over time, but, though Reese and Wadsworth[4] state that they progress, their natural history is not fully known.

Discussion

The structures described here are the same as those described by Vogt[1 2] and Reese and Wadsworth[4] in the living subject. They are rare before the fifth decade and occupy chiefly the perinuclear cortex. Retrodots are optically denser than the surrounding normal lens and are birefringent.

Brightly reflective structures in the lens[11] have been attributed to cholesterol[12 13] or to a non-crystalline lamellar structure[14] in dystrophia myotonica or in 'christmas tree' cataract.[15] However, crystalline or pseudocrystalline structures have also been demonstrated by several workers in the nuclei of hypermature or morgagnian cataracts[16–20] and in association with phacolytic glaucoma.[21–23] Vogt[2] observed punctate opacities with a crystalline appearance in vivo in hypermature cataracts, and these were studied in the same year by in vitro microscopy by Wessley,[24] who termed these objects spheroliths. They have been further studied in recent years.[25 26]

The chemical nature of these cystalline bodies has been demonstrated by a number of authors to be calcium oxalate.[17 18 21 23] Flocks *et al.*,[21] Zimmerman and Johnson,[17] Goldberg,[23] and Bron and Habgood[18] examined the bodies found in vitro within morgagnian lenses, while Pau[20] studied spheroliths known to be

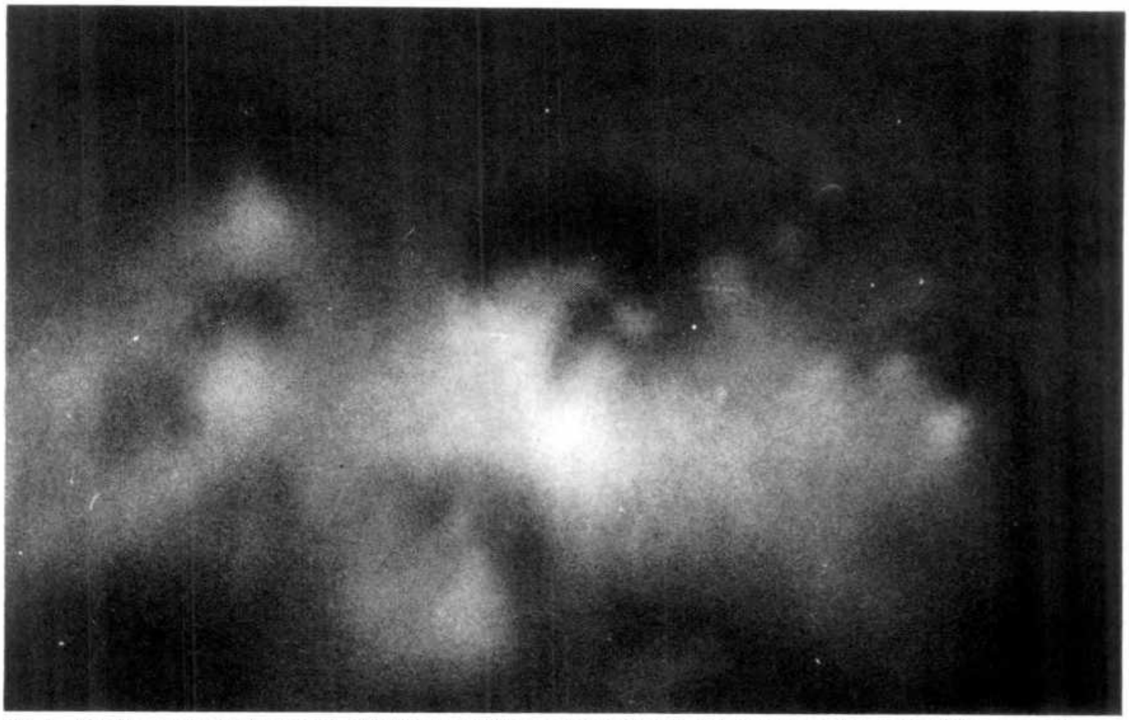

Fig. 7 *Photomacrograph by specular illumination of the anterior nuclear face showing retrodots as small elevations. (Brown macrocamera at a primary magnification of 15 times.)*

present in vivo. Harding *et al.*[27] identified bodies within fresh cataractous lenses in vitro documented by the stereo photographic procedure of the collaborative cataract research group (CCRG). The latter authors noted the value of crossed polarising filters in the system to make the features visible. Using energy dispersion x-ray analysis (EDXA), they found the opacities to be high in calcium, low in sulphur, and lacking in phosphate. Microchemical analysis suggested the presence of oxalate. Histologically the bodies were 'spheroidal' in cross section. They raised the question whether such opacities might be identified in the living patient, and it is our contention that the bodies which we have called retrodots are related to the spheroliths of the German literature and are identical to the calcium-containing, birefringent bodies observed by Harding *et al.*[27] We can regularly show that the bodies described by us as retrodots in vivo are strikingly birefringent in vitro in the extracted lens (Figs. 8a, b).

The bodies described here as retrodots are discus-shaped, being flattened from before backwards. This flattened shape is probably determined by the concentric lamellar arrangement of the lens fibres, which could affect either the direction of growth of these structures or mould their shape if they are sufficiently fluid at some stage. The birefringence of these structures suggests that they contain a birefringent, crystalline material probably identical to the oxalate bodies of morgagnian cataract (the spheroliths of the German literature) and the oxalate bodies observed by Harding *et al.*[27] But certain differences do exist. Spheroliths are described in the lens nucleus, while retrodots are found mainly in the deep lens cortex, but also in the nucleus. The difference here may merely be one of definition. As nuclear sclerosis advances, so the brunescent colour change often extends to affect the deep cortex. However, spheroliths found in a morgagnian cataract are distinctly spherical and therefore are morphologically different from retrodots. Also, where the retroillumination characteristics of spheroliths have been recorded, they have been described as dark, and in this characteristic too are clearly different from retrodots.[25] Since both lesions are birefringent it is tempting to conclude that they are related, and, since spheroliths are most common in association with advanced cataract, it is reasonable to hypothesise that the retrodots are a precursor of the spheroliths.

There thus now seems to be good evidence that the material within the retrodot is calcium oxalate, and it is reasonable to consider ascorbic acid as its source

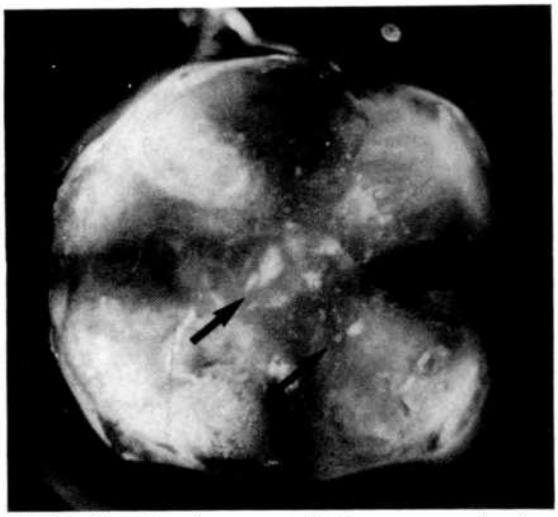

Fig. 8a *Retrodots demonstrated in the cataractous lens in vivo are shown here to be highly birefringent in the extracted lens under crossed polarisers (arrowed). Birefringence of the whole lens is visible as a dark 'Maltese cross'.*

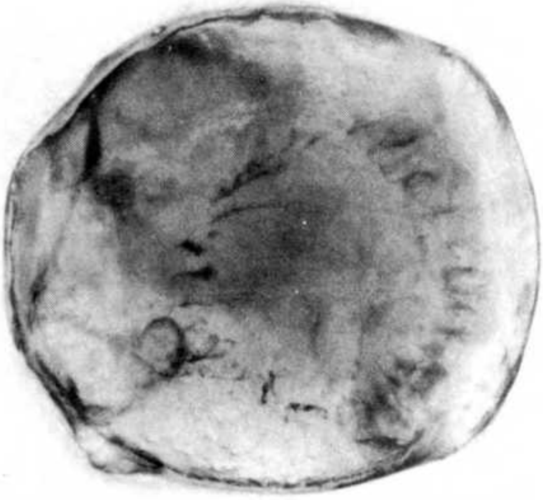

Fig. 8b. *Without crossed polarisers the retrodots are not visible in this system.*

for a number of reasons. Ascorbic acid is abundant in human adult aqueous and lens.[27-31] In man, monkey, and rabbit prenatal levels are low and similar to plasma levels (0·05 mM).[32] However, postnatal levels are about 20–40 times the plasma levels (1–1·8 mM)[32] as a result of active secretion by the ciliary epithelium.[33] In some animals of chiefly nocturnal habit aqueous ascorbate levels are low (rat, trace; galago, 0·03; and cat, 0·07 mM), and it has been suggested that this is an adaptive difference reflecting an antiphoto-oxidative role of ascorbic acid in the eye.[34 35] Differences in ascorbate levels between lens and plasma do not depend on the ability to synthesise ascorbate, since rat lens levels are high, though there is no synthetic ability. Human lens levels have been said to exceed aqueous levels, but a mechanism for this is not clear.[35 36]

Ascorbic acid has a role as a cofactor in a post-translational step of collagen biosynthesis,[36] and in the maintenance of intercellular ground substance material.[37 38] Apart from this it is a component of a protective system against damage by oxygen and free radicals derived from photo-oxidation. The most significant of these systems is the glutathione system in conjunction with glutathione peroxidase, superoxide dismutase, and ascorbic acid.[39] A number of workers have noted a drop in lens ascorbate levels associated with age,[29 30] and in experimental cataract and human senile cataract.[40-53] There is a greater fall in mature than immature cataractous lenses. Some workers have proposed an aetiological role for this fall of ascorbate in senile cataract with dietary implications, while others have denied this.[45 52 53] Lens vitamin C falls to low levels early in the course of microwave cataract.[54 55] Glutathione levels are also reduced in senile cataract,[49 50 52 56 57] along with levels of glutathione reductase and protein thiols,[56] and the degree of fall correlates with increased nuclear brunescence.[58]

It is accepted that loss of reduced glutathione on exposure to photo and other oxidative stresses results in the formation of protein-protein disulphides and mixed (protein-glutathione) disulphides, with the formation of light-scattering insoluble and high molecular weight crystallin aggregates.[58] A fall in glutathione levels in the lens is the earliest change to occur in cataract caused by ionising radiation when vitamin C levels are unchanged.[57] Consul and Nagpal[52] demonstrated a simultaneous fall in vitamin C and glutathione in cataractous lenses (for example: normal vitamin C, 24·1 mg/100 g wet weight; immature cataract, 6·7 mg/100 g; mature, 5·8 mg/100 g; normal glutathione, 354·3 mg/100 g; immature cataract, 29·6 mg/100 g; mature, 3·2 mg/100 g.[52] Other workers have also noted this combined fall of glutathione and vitamin C in cataract.[49 50 59] This could be construed as a response to oxidative stress and also represents a state whereby such lenses would be more susceptible to oxidative stress than normal lenses. In the normal lens the level of ascorbate is about 1 μmol/g of lens, which is one-tenth the concentration of GSH.[57] It is of interest that in vitro ascorbate oxidation is inhibited by the thiol groups of glutathione, cysteine, or lens proteins, while conversely glutathione is oxidised when incubated with ascorbate but not when incubated alone.[57]

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e dosage may be safely increased to 2 drops every hour. Care should be taken not to discontinue therapy prematurely.
ications, Warnings, etc. CONTRA-INDICATIONS. Acute superficial herpes simplex keratitis. Fungal diseases of ocular
Vaccinia, varicella and most other viral diseases of the cornea and conjunctiva. Tuberculosis of the eye. Hypersensitivity
stituents of this medication. **Warnings** Steroid medication in the treatment of herpes simplex keratitis (involving the
quires great caution; frequent slit-lamp microscopy is mandatory. Prolonged use may result in glaucoma, damage to the
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ocular infections from fungi or viruses liberated from ocular tissue. In those diseases causing thinning of the cornea or
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the age group two years or below. This preparation contains benzalkonium chloride and should be used with caution in
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3. **Precautions** As fungal infections of the cornea are particularly prone to develop coincidentally with long-term steroid
s, fungus invasion must be suspected in any persistent corneal ulceration where a steroid has been used or is in use. Intra
sure should be checked frequently. **Adverse Reactions** Glaucoma with optic nerve damage, visual acuity or field defects,
ubcapsular cataract formation, secondary ocular infection from pathogens liberated from ocular tissues, perforation of
Local side-effects of steroid therapy, ie skin atrophy, striae and telangiectasia, are especially likely to affect facial skin.
utical Precautions Protect from freezing. **Legal Category** POM. **Package Quantities** Supplied in plastic dropper
5ml and 10ml. Basic NHS cost (as at July 1984) 5ml £1.78, 10ml £2.83. PL 0426/0028. Full prescribing information is available

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above and, in addition in diseases due to micro-organisms resistant to neomycin, infection may be masked enhanced or activated b
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or other untoward reactions occur, discontinue the medication. **Precautions** Patients with histories of herpes simplex keratitis
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topical steroids during pregnancy has not been substantiated. Local side effects of steroid therapy, ie skin atrophy, striae and
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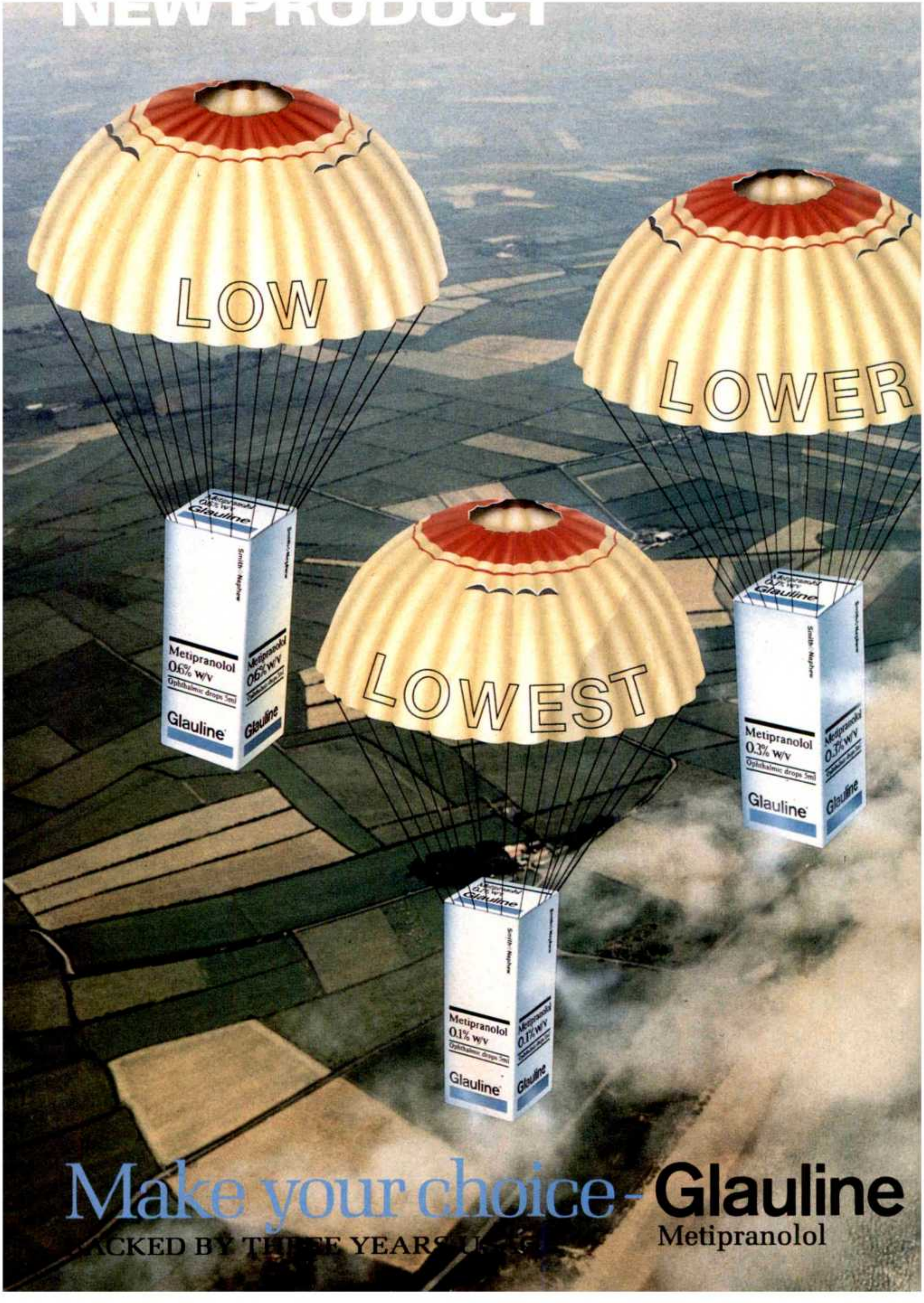
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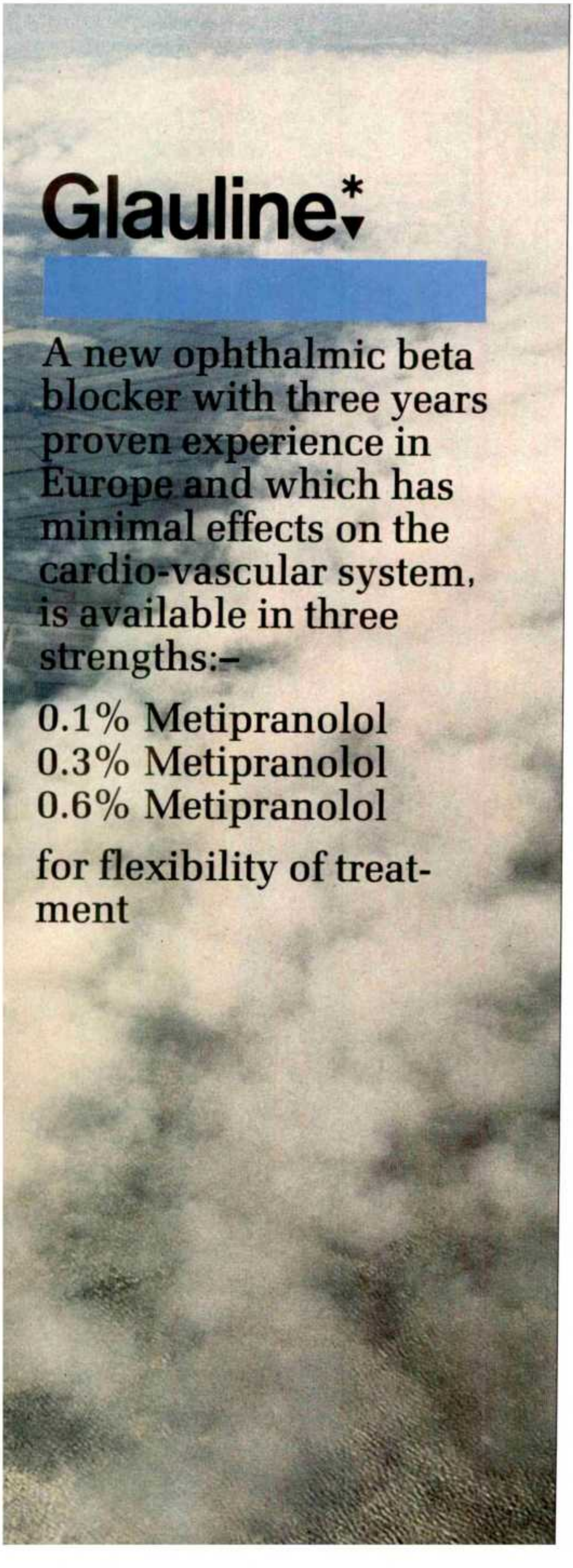

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USES
Glauline is a beta adrenoceptor blocking agent used in the topical treatment of chronic open-angle glaucoma and other conditions in which intra-ocular pressure is elevated above normal levels.

DOSAGE AND ADMINISTRATION
The recommended dosage is one drop instilled into the affected eye twice daily. Newly diagnosed patients should be treated in the first instance with Glauline 0.1%, changing to a higher strength if adequate control is not achieved or maintained. Patients on existing therapy, whether or not this is to be continued, should receive 0.3% Glauline and the intraocular pressure of all patients should be monitored regularly (e.g. every 4-6 weeks).
Use of the 0.6% strength is only recommended in patients who are not controlled on the lower strengths of Glauline.

CONTRA-INDICATIONS, WARNINGS ETC.
The use of Glauline is not recommended in patients with obstructive airway disease, cardiac failure or hypersensitivity to metipranolol. Beta blockers should not be given with verapamil and neither drug should be administered within several days of discontinuing the other. As absorption into the circulation is possible, Glauline should be used with caution in patients already receiving similar drugs by mouth. In particular, care should be taken in patients with sinus bradycardia and greater than first degree heart block.
Although there is no evidence to suggest that metipranolol has teratogenic properties, its use during pregnancy should be avoided, unless the potential benefits are considered to outweigh the possible hazards. No clinical trials in children have been carried out. Glauline should not be used in patients fitted with soft (hydrophilic) contact lenses.

PHARMACEUTICAL PRECAUTIONS
Glauline should not be diluted or dispensed from any container other than the original bottle. It is potent for three years unopened, but as with other eye drops the contents of each bottle should be discarded one month after opening.

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Glauline is supplied as a sterile ophthalmic solution in a 5ml plastic dropper bottle.

FURTHER INFORMATION
Glauline has little or no effect on pupil size or accommodation.
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The latter action may relate to the formation of hydrogen peroxide when ascorbate is oxidised.[60] However, in other circumstances vitamin C is a powerful inhibitor of oxidative processes, such as the photo-oxidation of tryptophan and other aromatic amino acids.[61]

Support for a role of ascorbate protecting against photo-oxidative and other oxidative stress comes from various sources. Varma *et al.* demonstrated a protective role for ascorbate against light-induced damage to the epithelial cation pump of the rat lens[62] and Zigman *et al.* demonstrated that ascorbate inhibited lens darkening in experimental ultraviolet cataract.[63] A comprehensive series of studies by Tso has shown a protective effect of dietary supplementation with ascorbic acid, L-dehydroascorbic acid and sodium ascorbate, against the photoreceptor damage induced by intense light in the rat retina. This group have demonstrated a light induced fall in retinal ascorbate in rat, guinea pig, and monkey retina. They conclude that ascorbate functions as an antioxidant molecule in the retinae of these species.[64–69]

At biological pH L-ascorbic acid is readily and reversibly oxidised to L-dehydroascorbate and can be further degraded through 2,3 diketo-L-gulonic acid to L-xylonic and L-lyxonic acid (by a decarboxylation, or to L-threonic acid and oxalic acid (by oxidation).[70 71] Although oxalic acid can be converted to formate and carbon dioxide by bacteria, plants, and certain animals, it is a metabolic end product in mammalian systems, and 89–99% of an administered dose in humans is excreted in the urine. Ascorbate accounts for about 35–50% of oxalate excretion; but glyoxylate is the major pathway of biosynthesis.[70] It is this last pathway which is affected in primary oxalosis or oxaluria (types I and II), in which renal and other tissue deposition of oxalate is accompanied by oxaluria. The eye is not involved in this condition. Two minor sources of oxalate in mammalian systems include tryptophan—probably by interconversion with serine and then to glyoxylate—and tyrosine or phenylalanine, presumably via auto-oxidation of their α-keto-analogues.[70]

Secondary oxaluric states occur after ingestion of ethylene glycol (a precursor of glyoxylate)[72] in pyridoxine deficiency, because of a reduced removal of glyoxylate through transamination to glycine,[73] and after ileal resection, possibly because of bacterial conversion of bile glycocholate into glyoxylate, and increased absorption.[70]

Oxalate retinopathy has been encountered clinically in a patient who received methoxyfluorane anaesthesia.[74] Methoxyfluorane is readily metabolised to glyoxylate.

Experimental oxalate retinopathy was also studied by van Heyningen and Pirie after naphthalene administration in the rabbit.[75] Naphthalene toxicity consists of a cataract accompanied by profuse oxalate deposition in the retina and vitreous. van Heyningen and Pirie proposed that 1,2-naphthoquinone is a metabolite of naphthalene, which oxidises ascorbic acid to oxalate and is itself reduced to 1,2-dihydroxy naphthalene. This is strong evidence for the possibility of oxalate formation in the living eye by oxidation of ascorbate. Lens ascortage falls in naphthalene cataracts,[75] but oxalate levels do not appear to have been measured in this condition. Vitamin C feeding has an equivocal effect on naphthalene cataract.[76]

A major feature of naphthalene cataract, apart from the development of opacity, is a brown discolouration, which has been attributed to the presence of naphthoquinone-protein compounds within the lens.[77–79] Another possibility could be the formation of non-enzymatic brown adducts between ascorbate and lens crystallins and other proteins. Bensch *et al.*[80] have demonstrated that ascorbic acid will form adducts with bovine crystallins or serum albumin with the same fluorescence excitation and emission spectra as the yellow-brown glycosylation products formed by glucose and other aldoses. (This latter reaction involves Schiff-base formation between an aldol group of glucose and amino groups of protein and subsequent stabilisation of the aldimine bonds by the Amadori rearrangement.[81] This is followed by a 'browning reaction', leading to stable, yellow-brown products.[81 82] These stable, covalently linked adducts have similar fluorescence spectra to chromophores extracted from human cataractous lenses. Bensch *et al.*[80] point out that ascorbate forms condensation products with proteins at a rate faster than that shown by common aldoses. Furthermore, outside the diabetic state, lens ascorbic acid levels are much higher than lens glucose, which should encourage brown-adduct formation from ascorbate. Such adducts have been proposed to account for the insoluble brown chromophore found in brunescent lenses.

These various accounts give the opportunity to propose a coherent hypothesis relating cataractous events occurring in and around the lens nucleus, supporting a general role for oxidative stress mechanisms. Three forms of lens change may be seen in the region of the nucleus. Retrodot lens opacities may be seen on their own or in combination with 'nuclear sclerosis.' Nuclear sclerosis may be either a colourless scattering opacity, a yellow to brown opacity, or a mixed opacity where scattering and colour changes are both seen. From what has been said above it may be inferred that the presence of retrodots implies that the lens has suffered oxidative stress which has oxidised ascorbic acid to oxalate.

The ascorbic acid content of the lens could be reduced. Pure, scattering sclerosis could be ascribed to a series of events following adduct formation between, say, lens crystallins and cyanate (carbamylation), with the resulting conformational changes exposing protein thiols. A decreased protective system against oxidate stress—for example, decreased levels of reduced glutathione—would expose lens crystallin thiols to oxidation, encouraging high molecular weight aggregate formation and a non-brunescent scattering type of opacity. Brunescent changes would be attributed at least in part to the formation of non-enzymatic brown adducts, to which oxidised ascorbate would make a major contribution in non-diabetics and glycosylation an increasing contribution in diabetics.

New techniques of classification and examination of the lens and cataract make it possible to explore these hypotheses clinically as well as biochemically. We are engaged in an epidemiological study of lens opacities and will be able to quantify and correlate the features discussed. In patients coming to lens extraction further correlations will be made between the content of ascorbate and its metabolic products, including oxalate, and the morphological features of the cataracts.

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Host, microbial, and pharmacological factors affecting the outcome of suppurative keratitis

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SUMMARY A review of 87 cases of microbial keratitis in South Australia was made to determine the factors which influence the outcome of the disease. The preceding pathology and the extent of ulceration at presentation were found to be significant, while the presence of hypopyon was less important. Infection with *Pseudomonas aeruginosa* was most likely to result in a poor outcome. Most patients had a history of traumatic injury, herpes simplex keratitis, or a corneal graft. The choice of gentamicin and a cephalosporin as appropriate initial therapy in Australia was supported. The results are discussed with reference to current research objectives.

Microbial keratitis is a common sight threatening disease which occurs in all parts of the world.[1] Rational treatment involves identification of the causative agent and institution of specific antimicrobial chemotherapy. This demands clinical suspicion of a microbial cause for keratitis, knowledge of the likely agents in a particular community, reliable microbiological investigation, and the availability of effective antibiotics. Even under optimal conditions treatment is not invariably successful.

In an attempt to identify factors which may affect outcome we have reviewed the course of the disease in patients presenting to the Department of Ophthalmology at Flinders Medical Centre. Although a number of ophthalmologists have been involved, treatment received has been consistent and according to strict protocol.

Flinders Medical Centre is situated in suburban Adelaide. As the Department of Ophthalmology functions both as a primary care facility and a referral centre for the state of South Australia and beyond, the patients described in this study either presented for primary care or were referred by other ophthalmologists. Although management protocols are firmly established and every attempt has been made to keep consistent records, this study has the disadvantages of being retrospective. Such a limited approach, however, is justified in the case of this disease because of the difficulty of carrying out prospective controlled clinical trials.

Patients and methods

Between August 1980 and February 1986 material was collected from the corneas of 164 patients for microbiological study. All patients were investigated in whom there was a defect in the corneal epithelium and inflammation in the underlying corneal stroma. Thus both patients in whom microbial infection was strongly suspected as the cause of inflammation and others in whom alternative explanations were possible were similarly tested.

A standardised method of specimen collection was employed. Corneal scrapings were taken in the Eye Clinic or in the ward with an operating microscope or a slit-lamp. Specimens were collected with a platinum spatula. Two horse blood agar plates, a chocolate agar plate, a Sabouraud's agar slope, two glass slides, a cooked meat-glucose broth, and two brain-heart infusion broths supplemented with vitamin K, haemin, and nicotinamide adenine dinucleotide (NAD) were inoculated. The Sabouraud's slope was incubated at 30°C for up to one month for culture of fungi. The other media were incubated at 37°C for two days. One blood plate and the cooked meat broth were incubated anaerobically. The remaining media were incubated in 5% carbon dioxide/air. The slides were used for Gram and Giemsa stains.

Organisms were identified by standard microbiological methods as given in the *Manual of clinical microbiology*.[2] Susceptibility to antimicrobial agents was determined by a modified Kirby-Bauer technique.[3] A growth was considered significant if

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organisms were seen on microscopy and grew on at least one medium, or if no organisms were seen on microscopy yet growth occurred on at least two media.

Results

A significant growth of organisms was isolated 87 times from 78 eyes of 76 patients over the 5½-year period. There were 50 males and 26 females, and their ages ranged from 14 months to 96 years with two distinct peaks in age distribution, one in early adult life and one in old age (Fig. 1).

Microbial keratitis occurred predominantly in eyes with existing pathology. Predisposing factors were identified in 84% of the patients (Table 1). Herpes simplex virus (HSV) keratitis was the most common pre-existing disease, these patients having an average age of 59 years. In younger patients (average age 44 years), trauma, including corneal lacerations, abrasions, and foreign bodies, was more common. This difference in corneal status contributed to the two peaks in age distribution. The four cases with exposure ulcers were stroke or comatose patients with inadequate lid closure.

Table 1 *Pathology prior to microbial keratitis*

	*No. (%) of eyes**
Trauma	14 (17·9)
HSV keratitis	12 (15·4)
HSV keratitis and corneal graft	7 (9·0)
Corneal graft	6 (7·7)
Exposure ulcer	4 (5·1)
Bullous keratopathy	3 (3·8)
Herpes zoster ophthalmicus	2 (2·6)
Sjögren's syndrome	2 (2·6)
Bowen's procedure to limbus	1 (1·3)
Vernal catarrh	1 (1·3)
Soft contact lens wear	1 (1·3)
Trauma and corneal graft	1 (1·3)
Stevens-Johnson syndrome	1 (1·3)
H. zoster ophthalmicus and corneal graft	1 (1·3)
Systemic lupus erythematosus	1 (1·3)
Lens extraction and IOL implant	1 (1·3)
Multiple myeloma and malnutrition	1 (1·3)
Epithelial dystrophy	1 (1·3)
Prematurity	1 (1·3)
None apparent	11 (14·1)
Not known	6 (7·7)
Total	78

*In 76 patients. Two patients had infections in both eyes; one had Sjögren's syndrome and the other had previous grafts for keratoconus.

The organism responsible for keratitis comprised about 30 species in 21 genera of bacteria, fungi, and amoebae (Table 2). Bacteria were responsible for 77 cases, fungi for eight, and free-living amoebae for two. All patients were from South Australia except four; three came from Queensland and one from Singapore, all of whom were infected with filamentous fungi. *Staphylococcus aureus* was the most frequently isolated organism, being responsible by itself for 23% of the cases. As *Staphylococcus epidermidis* was isolated alone in 12 cases (13·8%), staphylococcal species were responsible for more than a third of the infections. An obligate anaerobe, *Peptostreptococcus anaerobius*, was isolated in only one case. *Pseudomonas aeruginosa* was the most frequently encountered Gram-negative bacillus (GNB), being responsible for 10·3% of the infections. Two or more organisms were cultured from a cornea on 11 occasions (12·6%). In two cases *Acanthamoeba* species were isolated; one of these patients had splashed wood alcohol into his eye and the other had a three-year history of HSV keratitis.

The Gram stain correlated with the culture result in 58% of cases (Table 3). Of the eight instances

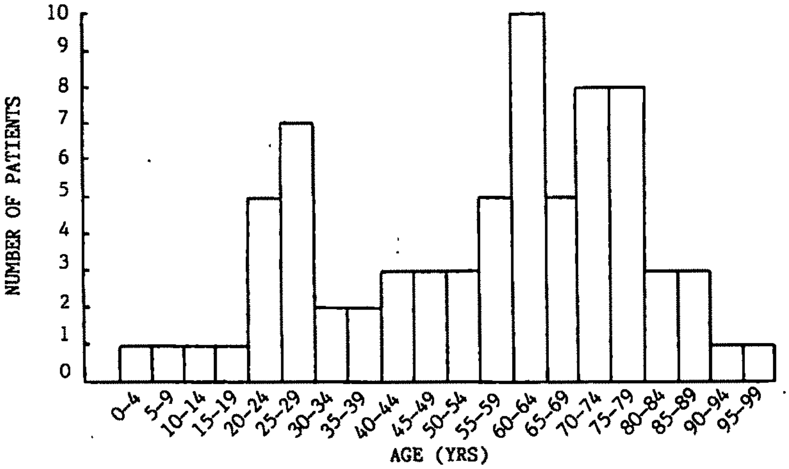

Fig. 1 *Age distribution of patients with microbial keratitis.*

Table 2 *Organisms isolated from cases of microbial keratitis*

	No. (%) of isolates
Gram-positive cocci	
Straphylococcus aureus	20 (23·0)
Staphylococcus epidermidis	12 (13·8)
Streptococcus pneumoniae	5 (5·7)
Viridans streptococci	4 (4·6)
Peptostreptococcus anaerobius	1 (1·1)
Staph. aureus and viridans streptococci	2 (2·3)
Staph. epidermidis and viridans streptococci	1 (1·1)
Gram-positive bacilli	
Corynebacterium spp.	5 (5·7)
Gram-negative bacilli	
Pseudomonas aeruginosa	9 (10·3)
Moraxella spp.	4 (4·6)
Haemophilus influenzae	2 (2·3)
Klebsiella oxytoca	2 (2·3)
Proteus mirabilis	1 (1·1)
Serratia marcescens	1 (1·1)
Pseudomonas maltophilia and *Achromobacter* spp.	1 (1·1)
Mixed	
Staph. epidermidis and *Corynebacterium* spp.	2 (2·3)
Staph. aureus and *Proteus mirabilis*	1 (1·1)
Viridans streptococci and *Moraxella* spp.	1 (1·1)
Viridans streptococci and *Corynebacterium* spp.	1 (1·1)
Str. pneumoniae, Staph. aureus, and *Moraxella nonliquefaciens*	1 (1·1)
Escherichia coli, Enterobacter cloacae, Hafnia alvei, Candida krusei, and *Pseudomonas acidovorans*	1 (1·1)
Fungi	
Candida albicans	2 (2·3)
Fusarium spp.	3 (3·4)
Acremonium sp.	1 (1·1)
Alternaria sp.	1 (1·1)
Aspergillus fumigatus	1 (1·1)
Amoebae	
Acanthamoeba spp.	2 (2·3)
Total	87

where organisms were seen on the smear but did not grow, GNBs were seen six times and Gram-positive cocci (GPC) twice. In three of the six instances the GNBs were large coccobacilli of the *Moraxella* type.

Data for antimicrobial susceptibility of commonly isolated organisms are shown in Table 4. All isolates of each bacterial species were sensitive to at least two antibiotics. Cephradine was effective in vitro against all isolates except some *P. aeruginosa*. Gentamicin was effective against all isolates except some *Streptococcus pneumoniae*.

Table 3 *Correlation of Gram stain with culture result*

Organisms cultured seen in Gram stain	45/77 (58·4%)
Some organisms cultured seen in Gram stain	3/77 (3·9%)
Organisms not seen	21/77 (27·3%)
Other organisms seen (with or without cultured organisms)	8/77 (10·4%)

After isolation of the organism responsible the patients received specific antimicrobial chemotherapy and most (70%) also received topical corticosteroids. Corneal transplantation was performed on 18 eyes.

The outcome of treatment of microbial keratitis is given in Table 5. Of the corneal grafts 12 were successful, and one failed owing to allograft rejection. In three cases infection recurred in the grafted eye, but the organisms responsible were other than those which had caused the initial infections. Each of these patients had a history of herpetic ocular infection. All six patients with filamentous fungal infection received a graft; a successful result was achieved in four cases.

Of the 72 eyes for which the outcome was known 13 (18·1%) were lost. As well as the recognised pathogens the organisms that contributed to the loss of eyes included *Corynebacterium* species, *Staphylococcus epidermidis*, and *Streptococcus sanguis* type II. In 14 eyes (19·7%) there was complete resolution of disease and in 25 (35·2%) the infection resolved to useful vision, defined as the hand motion to count fingers range. When the number of cases in which the disease resolved to useful vision or better is added to the number of successful grafts, it can be seen that a good outcome was achieved for 72% of the eyes.

Treatment was successful for all patients with a history of corneal trauma but for only 42% of patients with a history of HSV keratitis (Table 6). On χ^2 analysis the frequency of a poor outcome for patients with a history of HSV infection was shown to be significantly greater than for those with a history of trauma ($p<0\cdot005$). In comparison with all other previous pathology the probability that the greater frequency of a poor outcome following HSV infection is due to chance is about 6%.

For 22 patients the outcome of treatment of

Table 4 *Percentage of isolates sensitive to various antibiotics*

	Staph. aureus	*Staph. epidermidis*	*Str. pneumoniae*	*Coryne.* spp.	*P. aeruginosa*	*Moraxella* spp.
Penicillin	23	0	75	100	—	100
Cephradine	100	100	100	100	33	100
Chloramphenicol	100	75	100	80	20	100
Gentamicin	100	100	33	100	100	100
Tobramycin	—	—	—	—	100	—
Carbenicillin	—	—	—	—	100	—

Table 5 *Outcome of microbial keratitis*

	No. (%) of eyes
Eye removed	13 (16·7)
Corneal graft—successful	12 (15·4)
—rejected	1 (1·3)
—recurrence of infection	3 (3·8)
Failure of previous graft	4 (5·1)
Recurrence of infection	2 (2·6)
Resolution to useful vision	23 (29·5)
Complete resolution	14 (17·9)
Not known	6 (7·7)
Total	78

Table 6 *Relationship of previous pathology to outcome of microbial keratitis*

	No. (%) of patients	
	Trauma	*HSV*
Eye removed	0	4 (21·1)
Corneal graft—successful	2 (13·3)	4 (21·1)
—rejected	0	1 (5·3)
—recurrence of infection	0	2 (10·5)
Failure of previous graft	0	2 (10·5)
Recurrence of infection	0	2 (5·9)
Resolution to useful vision	7 (46·7)	4 (21·1)
Complete resolution	6 (40·0)	0

microbial keratitis was not successful. This group had a total of 26 culture-proved infectious episodes in 23 eyes. Additional data are given in Table 7. Of these patients 70% had had either HSV keratitis or a previous graft, or both, compared with 38% overall. The extent of ulceration at presentation was classified as slight if less than 10% of corneal area was suppurating, moderate if 10–30% was suppurating, and severe if more than 30% was involved. The association between a patient presenting with moderate or severe ulceration and a poor outcome was significant ($p<0{\cdot}05$). The presence of hypopyon did not significantly affect outcome. *P. aeruginosa* and mixed infections predominated among the patients having a poor outcome, though the total number of cases is not sufficient to show any significant associations. A poor outcome could not be correlated with the use of inappropriate antibiotics before the antimicrobial sensitivity data became available.

A successful outcome was achieved in 69% of cases where topical corticosteroid was included in the therapy compared with 78% where no steroid was given. However, these figures are biased by the consideration that the more severe cases generally received steroid. Infection recurred in 13% (7/54) of patients given steroid compared with 0% (0/23) of patients who did not receive steroid.

Discussion

The pattern of disease in this series of cases was similar to that seen in other studies from urban communities in temperate climatic zones.[4-6] Thus the range of organisms, antimicrobial sensitivity, and predisposing disease were perhaps to be expected. Although there have been no published reports of the outcome of microbial keratitis, less than optimal results are commonly experienced by all ophthalmologists dealing with this condition.

Infection is often responsible for ultimate loss of sight in an eye ravaged over a period of time by chronic relapsing disease consequent upon epithelial disruption and stromal derangement. The frequency of poor outcome of bacterial infection in patients who have chronic herpetic keratitis, and who often have had previous corneal surgery as well, attests to this. It also emphasises the role of the intact epithelium as a primary defence mechanism; corneal infection seldom occurs in otherwise healthy eyes.

Only one case of infection attributable to contact

Table 7 *Data on patients with poor outcome**

Average age (yrs)	*Preceding pathology†*		*Extent of ulceration†*		*Hypopyon present†*	*Organisms†*		*Antibiotics used†*	
60·3 (53·4)	HSV and graft	26	Slight	9 (43)	42 (24)	*P. aeruginosa*	23 (6)	Correct	92 (80)
	HSV	17	Moderate	57 (47)		*Staph. aureus*	19 (31)	Incorrect	0 (0)
	Graft	17	Severe	17 (10)		*Coryne.* spp.	8	None used	0 (16)
	Graft and SCL	4	Unknown	17 (0)		*Str. pneumoniae*	8	Unknown	8 (4)
	H. zoster and graft	4				*Moraxella lacunata*	4		
	Bullous keratitis	4				*H. influenzae*	4		
	SLE	4				*Serratia marcescens*	4		
	Cat. extract and IOL	4				*Str. sanguis* II	4		
	None apparent	17				*Staph. epidermidis*	4		
						Alternaria sp.	4		
						Mixed	19 (4)		

*Eye removed, graft rejected, recurrence of infection, or failure of a previous graft.
†Expressed as % of cases. Figures in brackets are for patients with successful outcome.
SCL=soft contact lens. SLE=systemic lupus erythematosus. IOL=intraocular lens.

lens wear was encountered, though perhaps more might have been expected in view of the findings of others.[7] The patient concerned had been wearing an extended-wear soft lens over an aphakic corneal graft, and had received no routine care for the lens or the eye. Lax aftercare by the ophthalmologist or optometrist and non-compliance on the part of the patient are the major sources of risk to an eye wearing a contact lens. During the period of this study the Contact Lens Clinic at Flinders Medical Centre had as many as 200 patients with extended-wear lenses in its care at any one time.

The management of microbial keratitis was consistent over the five-year period of the study. Initial treatment was based on the Gram stain. If the Gram stain revealed GPCs, a first generation cephalosporin was given topically every hour, either 50 mg/ml cephradine or, more recently, cephazolin. If GNBs were seen, the patient was treated with 10 mg/ml gentamicin eye drops every hour. If no organisms were seen, no antimicrobial was given unless the clinical course of events strongly suggested bacterial infection, in which case both gentamicin and cephradine eye drops were administered. In the event of a negative culture, the clinical picture and laboratory results were considered after 24 hours, and the indications for therapy were reviewed after another Gram stain and culture. In all cases the appropriateness of the antimicrobial chemotherapy was reviewed as the results of culture and antimicrobial sensitivity tests came to hand, but with the clinical course always the dominant consideration. Topical corticosteroids were not begun until appropriate antibiotics had been given for 24 hours.

Although most failures to respond to treatment occurred in patients whose eyes were moderately or severely diseased at the time of presentation, either due to the existing predisposing condition or because of late presentation, poor results did occasionally occur unexpectedly. The prognosis may be unfavourable even when a patient presents early, the causative organism is identified, treatment is initiated, and susceptibility of the organism to the antimicrobial agent prescribed is confirmed. A number of factors may account for this. They relate to the interaction of organism, host mediated mechanisms, and pharmacological considerations.

Motivated by the results of this clinical study and the need to identify effective therapeutic regimens, we used a quantitative model in rats to investigate factors influencing the outcome of corneal infection.[8] Both bacterial and host cells were counted to compare the effectiveness of various treatments. This is necessary because both bacterial and host factors contribute to corneal destruction.[9-12]

The role of topical corticosteroids in microbial keratitis remains controversial. They do not compromise the effectiveness of appropriate antibiotics.[8, 13-15] However, when used for the treatment of pseudomonas keratitis without effective antimicrobial chemotherapy, the growth of organisms is significantly enhanced.[8, 16] In addition to replicating organisms both the breakdown products of dead bacteria, for example endotoxin,[17] and the products of tissue damage[18] are chemotactic for leucocytes. It would seem that corticosteroids may have an important role in limiting leucocyte recruitment occurring after microbial replication has been halted. In experimental *Staph aureus* keratitis prednisolone acetate was shown to add significantly to the anti-inflammatory effect of cephradine only late in the course of the infection.[8] Presumably at this time bacterial turnover is less and antimicrobial sensitivity is reduced, or, alternatively, non-replicative elements are responsible for leucocyte recruitment. In either case the suggestion is that in clinical practice little is to be gained by beginning topical corticosteroid therapy before the causative agent has been identified and specific antimicrobial chemotherapy instituted.

The essential element of treatment is delivery of adequate levels of antimicrobial agents to the focus of infection. Animal models are vital for determining the important aspects of drug kinetics in microbial keratitis.

Clinical studies suggest that currently employed doses of most antibiotics, applied topically or subconjunctivally, produce concentrations in the infected cornea that should be effective on the basis of minimum bactericidal concentration (MBC) tests. Carbenicillin,[19] cephalothin,[20] gentamicin,[21] and tobramycin,[22, 23] reach useful concentrations in the aqueous humour of patients with uninflamed eyes. Since the corneal concentration of an antibiotic is usually at least as high as the aqueous humour concentration,[24] and the presence of inflammation is known to increase antibiotic penetration into the anterior segment,[21, 25, 26] it is likely that the peak corneal concentration obtained in patients with suppurative keratitis is well above the MBCs of common pathogens. However, using rats we have found with cephradine that a 'passing through' effect can occur after topical administration on to an inflamed eye in which the tissue concentration fell to sub-MBC levels more rapidly than it would do in a normal eye.[26] This suggests that applications may need to be made more frequently than is usual.

An MBC must be considered only as a guide to the likely susceptibility of an organism to an antibiotic in vivo. It is determined with the use of organisms in logarithmic growth. However, in established infections the rate of cell turnover is less, so that the in-vivo MBC is in effect increased. We have found that the ratio of the antibiotic concentration required for 99% killing in the cornea to that in vitro is as high as 70:1 (presented at the Ocular Microbiology and Immunology Group Meeting, Atlanta, 1984).

Helpful as these animal studies are in increasing our understanding of microbial keratitis and its treatment, and difficult as it is to conduct clinical trials with a condition so diverse in its features, it is nevertheless necessary to pursue these trials if we are to improve our treatment of this important condition.

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Rational acyclovir therapy in herpetic eye disease

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SUMMARY Acyclovir has been widely used against the various manifestations of eye disease due to herpes simplex since it first became generally available in the UK nearly five years ago. This paper discusses the rational indications for its use, through considerations of its pharmacology and pharmacokinetics, and through results of the many clinical trials that have been carried out to investigate its effects since its clinical efficacy was first demonstrated in 1979.

Pharmacology and pharmacokenitics of acyclovir

The antiviral effect of acyclovir (ACV) was first described by Elion *et al.* in 1977[1] and subsequently by Schaeffer *et al.*[2] and Bauer *et al.*[3] It was the result of a systematic search for a specific antiherpes antiviral that exploits the fact that cells replicating these viruses, and particularly herpes simplex virus (HSV), are induced by the virus to produce thymidine kinase (TK). This enzyme activates ACV to the monophosphate–the first stage in the antiviral action of the drug that gives it an overall 3000 fold greater effect against HSV replication than against host cell synthesis. ACV itself is inactive, and its lack of toxicity not only allows prolonged topical therapy if necessary, but also systemic therapy–a fact that has made dramatic improvements in the management of herpes simplex virus infections in immunocompromised patients[4] and in those with herpes simplex encephalitis.[5] Toxicity from topical ocular therapy with idoxuridine, trifluorothymidine, and adenine arabinoside has become widely recognised.[6]

Topical application of ACV to the eye leads to therapeutic levels in the aqueous, even when the epithelium is intact,[7] though there have been suggestions that the stromal levels from 3% ointment may be suboptimal.[8] Oral therapy also leads to adequate levels of ACV in tears and aqueous,[9] for ACV crosses the blood-aqueous barrier.

It is not difficult to isolate strains of HSV that are ACV resistant: they are relatively or completely independent of TK.[10] These strains are, however, of low virulence, and clinical problems with ACV resistance have been minor; but they could increase with increasing use of the drug.

Rational use of acyclovir

PRIMARY HERPES SIMPLEX

Recent figures for the serological evidence of past (primary) herpetic infection vary between approximately 30%[11] and 80%,[12] but overt primary herpes occurs in only a small proportion of these individuals. By implication the condition is often very minor and self limiting, though ocular involvement may ensue,[13] and a severe disease can occur in immunocompromised[14] or atopic persons.[15] Neonates can suffer a severe ocular disease from HSV types 1 or 2, with conjunctivitis, keratitis, choroidoretinitis, optic neuropathy, and cataract.[16] Herpes encephalitis and a variety of other effects on the CNS can follow primary herpes.[17] Transneuronal spread can occur, so that the eye can be the site of recurrence from primary herpes elsewhere.[18, 19] This may also be one explanation for bilateral herpetic keratitis.

It is obviously essential to treat patients who have a serious form of primary herpes simplex. ACV is the drug of choice, since the systemic route will often be required. Topical treatment to skin lesions with IDU and even with ACV has little proved benefit, though topical treatment might be of benefit in preventing canalicular involvement, which has been shown to be a potent cause of canalicular obstruction in young people[20]; and topical treatment is clearly indicated if involvement of the globe follows the primary disease.

PREVENTION OF LATENCY AND RECURRENCE

There is no clinical evidence that treatment of primary herpes can reduce the likelihood of latency, or recurrence, although there is experimental evidence that the early administration of ACV following HSV inoculation in the eye can reduce the

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evidence of latency.[21] It is certainly the case that no means are yet available to eradicate latency once it has occurred. The presence of latent virus (of a particular strain) in the ganglion seems both to determine the clinical characteristics of the disease (in the eye)[22 23] and to inhibit the entry of virus of a different strain, although this latter effect is incomplete.[24] Evidence is also accumulating that the cornea (and perhaps other peripheral sites) may be the site of a 'latent' viral phase from which virus can be cultured[25] and seen to undergo replication in keratocytes.[26] None of these new data on latency offer any further direct hope of controlling it pharmacologically (if this is, indeed, desirable). In the meantime there is the possibility of long term prophylaxis with antiviral therapy. Obvious risks are the development of toxicity, and the development of resistant strains of HSV. No firm clinical data are available (apart from the special case where steroids provide the risk factor—considered elsewhere), but it is probably best to avoid long term prophylaxis, and to reserve short term prophylaxis for those individuals who can recognise trigger factors, using prophylaxis at these appropriate times. Experimentally, local or systemic ACV will prevent recurrences if it is given before the trigger factor appears.[27]

HERPETIC CONJUNCTIVITIS

HSV is a common cause of conjunctivitis.[13] It is often self limiting, though it can sometimes lead on to a keratitis resembling that due to adenovirus types 8 or 19, and it represents one part of the spectrum, ranging from an absence of symptoms or signs, to frank herpetic keratitis, that can result from repeated virus shredding. Since the outcome is uncertain when these patients are first seen, and since laboratory diagnosis is often not proved, it could be reasonably argued that antiviral therapy is appropriate, but there are no grounds for favouring any particular drug.

ULCERATIVE HERPETIC KERATITIS

The clinical trial that first showed that topical ACV was effective against dendritic ulcers was constructed in such a way that a minimum quantity of the drug was used.[28] A large number of trials have since been carried out comparing ACV with IDU, Ara-A and F_3T in patients with dendritic ulcers—using this very convenient microsystem to provide precise information on healing rates, healing percentages, toxicity, subsequent deep disease, and other complications. It may seem somewhat surprising that there has not been complete agreement in the results, though comparisons across different clinical trials are notoriously insecure. The trials of Coster *et al.*[29] and Collum *et al.*[30] are noteworthy in this regard: the first found no difference between ACV and IDU, whereas the second found ACV to be superior. The most cautious conclusion overall is perhaps that for patients with dendritic ulcers, which represent a simple task for the antiviral agent, no antiviral has been repeatedly demonstrated to be superior to any other. It could be argued that IDU should be used initially because it is effective and inexpensive and AVC should be reserved for possible future events such as disciform keratitis, where its particular advantages will be realised, or for circumstances where oral therapy is preferably to local,[31] ACV being effective by either route.[9] As already indicated, the primary use of ACV would be likely to select for ACV resistant strains of HSV, although these have not been a problem in clinical practice, perhaps because these strains are of low virulence.

Amoeboid ulcers present a more challenging problem for an antiviral than do dendritics, and their prognosis is worse in every way.[32] Clinical trials demonstrated a superiority of F_3T over Ara-A,[33] but ACV and Ara-A were recently shown to have equivalent effects.[34] Probably an important issue is the entry of the antiviral into the stroma, which will occur with F_3T when the epithelium is breached and with ACV even when it is intact, since there may be replicating stromal virus in these patients. Either drug is thus preferable to IDU or Ara-A. However, F_3T is not readily available in the UK, whereas it is marketed in the USA, but ACV is not.

Indolent ('metaherpetic') ulcers are perpetuated by such factors as antiviral toxicity, loss of corneal sensation, damage to basement membrane, stromal disease, and tear film inadequacy; and, by definition, viral replication is not occurring in the epithelium. This is not always the case in the stroma,[35] but even if the stromal disease is not being caused by viral replication, there may be a need for antiviral therapy to 'cover' steroid therapy. It seems reasonable to suggest that ACV should be the antiviral of choice in these patients: firstly, because it is the least toxic antiviral, and secondly because it has good ocular penetration.

KERATOUVEITIS

Numerous experimental and clinical studies have shown that deep keratitis and/or uveitis can be caused by viral replication or various immune mechanisms, and it is probably safest for the clinician to consider that both mechanisms are usually occurring, though to differing degrees in different patients, with the various forms of herpetic keratouveitis. Oh[36] has produced evidence that viral replication may occur in primary HSV uveitis but not recurrent disease (the latter being commoner clinically). But viral replication may undoubtedly be triggered off by steroid therapy,[37] both in the epithelium and in the stroma, and the use of a penetrating antiviral during steroid therapy for stromal disease appears logical.

Both steroids and ACV have been useful investigative tools in HSV keratouveitis. Collum and colleagues' demonstration[38] of the benefit from ACV and betamethasone compared with ACV alone in patients with disciform keratitis was the first trial to prove the short term value of steroids in this disease —a benefit nevertheless little doubted—and Colin *et al.*[39] found that ACV was superior to F_3T or Ara-A when used in combinaton with steroids for patients with deep disease. Sundmacher[40] has conversely shown a benefit from oral ACV in patients with virologically proved intraocular HSV disease, and Wilhelmus *et al.*[41] obtained a probable benefit from topical ACV compared with IDU in patients with herpetic uveitis. van Ganswijk *et al.*[42] found resolution of stromal keratitis within four weeks of starting ACV therapy in 35 patients with refractory deep disease, but Sanitato *et al.*[43] found no benefit from ACV in the management of 17 patients with herpetic stromal disease. Maudgal *et al.*[44] obtained good effects from a water soluble derivative of ACV (applied as drops) in the treatment of experimental keratitis produced by intrastromal injection of live virus. Maudgal's group found F_3T to be superior to 3% ACV ointment in this model, and suggested that a higher dosage of ACV than 3% ointment five times a day might be required for optimal stromal levels.

From these considerations it would appear logical to treat patients with HSV keratouveitis firstly with a penetrating antiviral alone, or even to use oral therapy for HSV uveitis, and to add as little steroid as possible if there is an inadequate response to the former. In the UK ACV is the drug of choice, and its lack of toxicity makes it particularly suitable for the long term therapy that is needed to accompany long term steroid therapy.

POSTERIOR SEGMENT DISEASE

Evidence is accumulating, particularly from vitreous specimens and retinal biopsy, that acute retinal necrosis and choroidoretinitis can sometimes be caused by HSV.[45] Grutzmacher *et al.* treated one such patient (virologically proved) with ACV successfully.[46]

The safety of ACV for intravitreal as well as oral use is particularly attractive. It may have a role in cytomegaloviris retinitis, though the in-vitro efficacy against CMV is not as strong as against HSV. Hydroxy ACV may prove to be superior.[47]

KERATOPLASTY

There has for some years been considerable discussion about the value (or otherwise) of using long term prophylactic antiviral therapy following grafting for herpes. Much of the earlier work inevitably referred only to IDU, and it was demonstrated that the risk of toxicity from this drug on the epithelium of the graft was unacceptably high.[48] However, Cobo *et al.*[49] showed that recurrence of herpetic epithelial disease was particularly likely in patients who developed a recurrence of inflammatory disease (whether due to rejection or herpes) following keroplasty, and this emphasised the need to cover the appropriately intensive steroid therapy that was given at this time. ACV (or perhaps F_3T, if available, and if not used for too long) would be the drug of choice for reasons already mentioned.

But what of long term ACV prophylaxis following grafting? It is certainly safe, but it may be undesirable to give ACV for many months (the incidence of recurrence remaining high for over a year postoperatively). It was shown by Kok van Alphen and Volker-Dieben[50] in a relatively small study that prophylaxis with ACV during the first months after operation did not appear to reduce the risk of recurrence. Probably the wisest action to take in the light of present knowledge is to give ACV prophylaxis to those patients deemed to be at a particularly high risk of recurrence, such as those requiring a high level of steroid, or those receiving a graft for therapeutic reasons (in an inflamed eye); and to give ACV prophylaxis as appropriate for later episodes of inflammatory disease; but to avoid long term ACV prophylaxis for patients in relatively low risk circumstances.

Conclusion

An attempt has been made in this article, by drawing on the appropriate data from the numerous workers, both clinical and non-clinical, involved in herpetic keratitis to guide the clinician in the rational use of acyclovir. It is no accident that so much of the data originated either from Barrie Jones's department or from those whose interest in herpetic eye disease was inspired by him. Acyclovir has already made a major contribution to patients suffering from this complex disease. Future developments are likely to include combination therapy—either with interferon, which has been shown to be more effective than ACV alone,[51 52] or a combination with antiviral drugs such as Ara-A that work at other sites, or ACV analogues that may offer advantages over the parent compound.

I am indebted to Mrs Julie Lawrence, who typed the manuscript.

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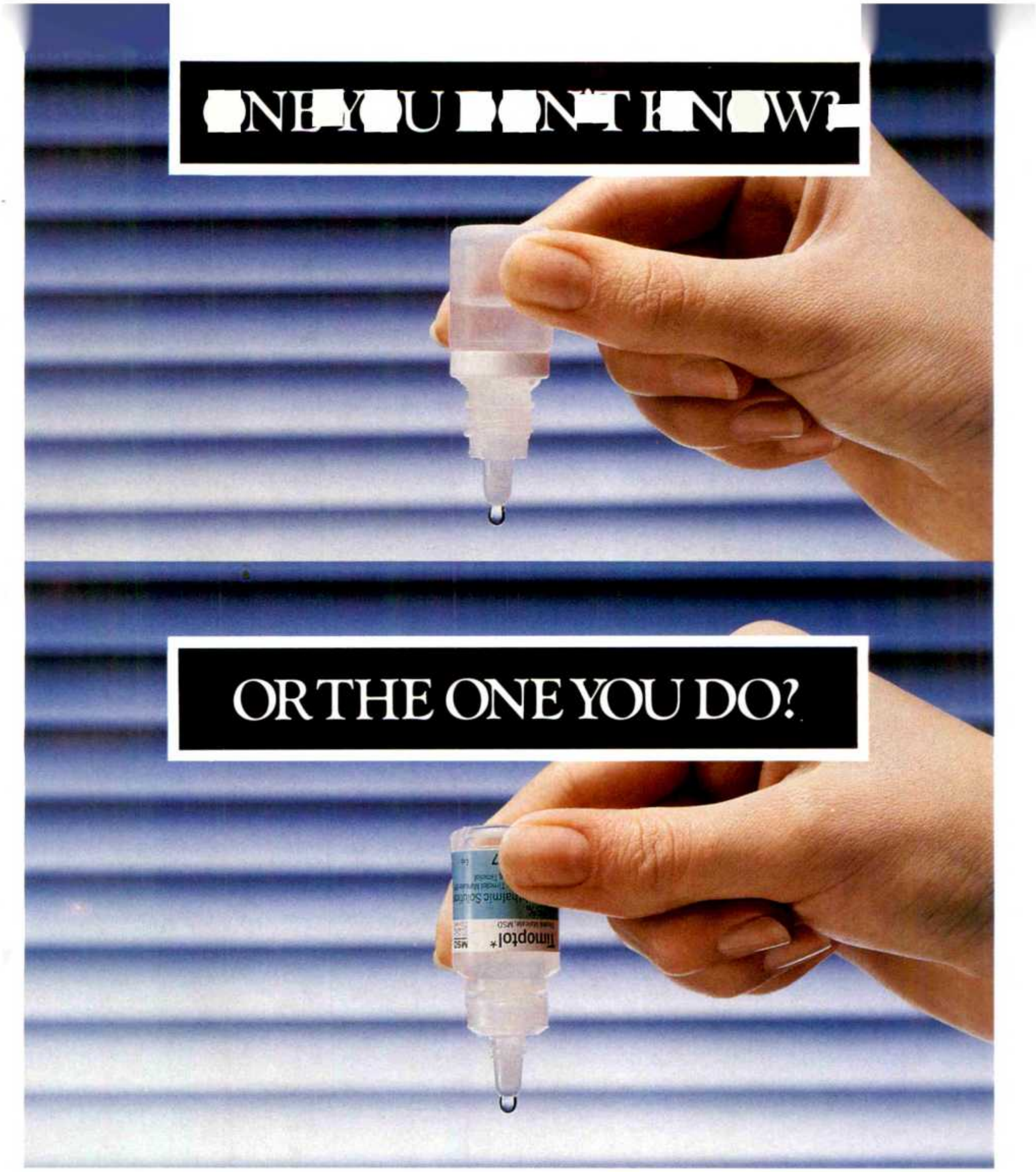

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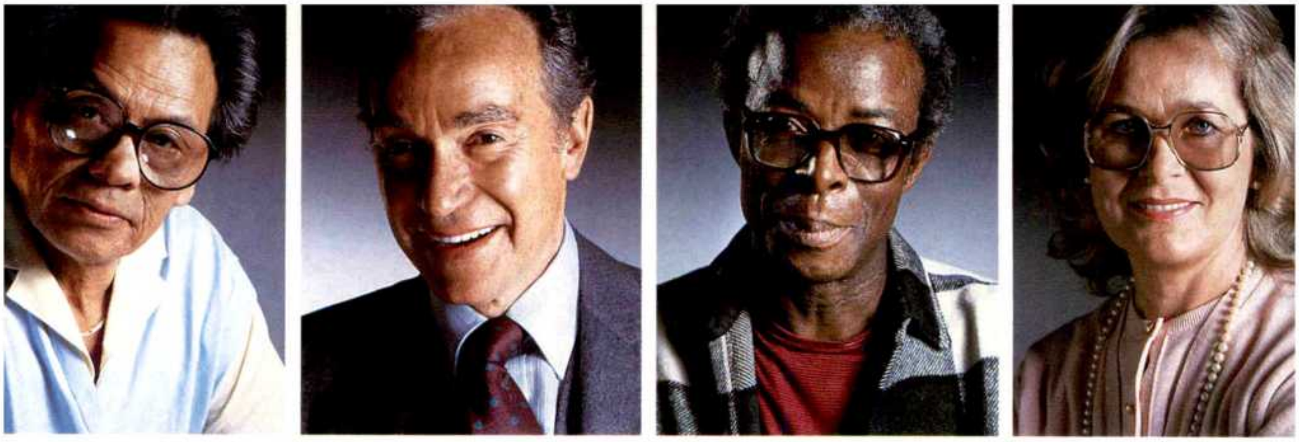

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Orbital decompression for severe dysthyroid eye disease

PETER FELLS

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SUMMARY Current methods of medical treatment of this difficult condition are briefly reviewed, with comments on the generally unsatisfactory response. Attention is therefore directed to surgical methods and a short history given of the various routes used for orbital decompression. The author's own results of transantral, and more recently ethmoidal, decompression are given, with a detailed description of the technique for the latter approach. An interesting frequent consequence of postoperative A pattern to the ocular movements is discussed in the light of Koornneef's concept of orbital fascial anatomy, and suggestions are made for its avoidance.

Severe dysthyroid exophthalmos is normally a bilateral disease in which both orbits are involved at the same time but in some patients the orbits are affected by the condition serially.

MEDICAL THERAPY

Over the years many methods of medical therapy have been tried in an attempt to control and reverse this sight threatening condition. The most successful of the medical treatments thus far has been the introduction of high dosage oral corticosteroids by Werner[1] in 1966, and doses of 120 mg per day of prednisolone are commonly given in this manner. Unfortunately this very high dosage has to be maintained for a number of months, and many patients find that the complications of the therapy make it unacceptable. The addition of azathioprine has not permitted a significant reduction in the dosage of prednisolone required.

More recent attempts at therapy have included plasmapheresis, in which the immunoglobulins are washed out of the patient's system.[2] Unfortunately when the plasmapheresis treatment ceases there is an enormous backswing and re-establishment of the condition, sometimes at more serious levels than those at the beginning of the therapy. The only successful use of plasmapheresis has been accompanied by high dose systemic prednisolone, and it is impossible to separate the effects of these two methods of therapy. Still more recently very encouraging reports for the use of oral cyclosporin A[3] have not been substantiated by other workers, including myself. Radiotherapy in carefully fractionated doses over a two-week period to the retrobulbar tissues in this condition does not yet have a regular place in the treatment of *acute* bilateral dysthyroid exophthalmos, because there is often a stage of initial increase in the swelling and chemosis, and again radiotherapy under these circumstances has to be accompanied by high doses of prednisolone. The role of radiotherapy with the linear accelerator in the less acute forms of still severe dysthyroid exophthalmos is being evaluated, but it appears to be offering worthwhile results.[4]

Acute severe dysthyroid exophthalmos threatens sight in two ways: the very high intraorbital pressure causes optic nerve failure, and it is probably mediated via compression of the blood supply to the optic nerve and the orbital tissues. The huge swelling of the extraocular muscles, which can so readily be visualised by CT scans[5] or magnetic resonance imaging techniques, shows the crowding at the orbital apex and the obvious effect on the many vital structures passing through that area. Vision may be under threat for other reasons. The gross proptosis in some cases prevents any degree of lid closure, so that there is chemosis, with drying of the cornea and conjunctiva, leading to exposure keratitis, corneal ulceration, and endophthalmitis. Here again there is an urgent need for more space to be created for the greatly increased orbital contents, namely the extraocular muscles and the orbital fat. Surgical decompression has been tried over many years in this condition. This article is a brief review of the

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techniques, with comments on my own current method of decompression and with a view to the future.

SURGICAL DECOMPRESSION ROUTES

Krönlein[6] used a lateral approach to the orbit in 1888 to remove certain orbital tumours. This method was adapted for use in orbital decompression, and Kennerdell and Maroon[7] have used it to allow dissection of all four orbital walls and give from 10-17 mm of improvement in the proptosis. The operation is often carried out on one side at a time, and many patients require simultaneous bilateral orbital decompression. It is not to be recommended as the best general approach to the condition.

In 1931 Naffziger[8] described orbital decompression into the anterior cranial fossa by removing the roof of the orbit on one side. The classical neurosurgical approach using frontal burr holes is employed, and the floor of the anterior cranial fossa is then removed, exposing the orbital contents. Access can be gained to both the lateral and the medial sides of the orbit by this approach, but there are many important anatomical structures in the superior orbit that have to be avoided when this route is used. Some cynics have claimed that the exophthalmos is replaced by pulsating exophthalmos, since the orbital contents are put into contact with the intracranial tissues, and the degree of decompression achieved is small.

In the 1930s a number of workers used the inferior orbital approach for decompression, and Walsh and Ogura[9] published a large series in which the Caldwell-Luc transantral approach allowed removal of the inferior and medial walls of the orbit for decompression. In 1967 Freedman and Barrie Jones[10] reported the use of this technique in a patient who had undergone Naffziger transfrontal orbital decompression three months previously but in whom visual acuity and the visual fields had deteriorated again, threatening his sight. These workers commented particularly on the advantages of binocular microscopical dissection via this rather deep hole to permit good removal of the medial wall of the orbit up to the level of the cribriform plate, and also of the medial half of the floor of the orbit. Professor Barrie Jones's earlier experience with surgery of the sinuses and facial bones enabled him to use this technique successfully.

I learned this method when working with Professor Barrie Jones on the Professorial Unit in 1968 and also his later technique of the extended lateral orbitotomy, which was used primarily to allow optimal access to orbital tumours.[11] It is worth noting in passing that this extended lateral orbitotomy was used on a patient with 30 mm of unilateral proptosis, which in those days was considered could not be the result of dysthyroid eye disease alone but must indicate a tumour within the orbit.[12] In fact the very extensive dissection carried out on the patient enabled us to identify the enormously enlarged rectus muscles and also to confirm that there was no orbital tumour. Improved diagnostic methods that are now available to us would prevent such surgery being undertaken for a dysthyroid patient.

DeSanto[13] is the present worker with the greatest experience of transantral decompression for thyroid eye disease, and he too uses the binocular microscope and removes all the orbital floor, both medial and lateral, to the infraorbital nerve. When all the bony tissue has been removed, the periosteum is then incised, allowing the decompression to occur.

I started by doing transantral decompression via the Caldwell-Luc approach for my first series of patients with dysthyroid eye disease.[14] With the first 15 transantral decompressions 12 were bilateral and ocular motor imbalance followed in four of them, but in only one of these was later ocular muscle surgery required for persistent diplopia. It is interesting to note that in a series of 200 transantral decompressions by DeSanto diplopia followed in 159 patients.

Material and methods

I have now changed to an anterior ethmoidectomy for decompression because I think that this allows better optic nerve decompression. The CT scan taken in the horizontal plane (Fig. 1) shows not only the crowding of tissue at the orbital apex but also the

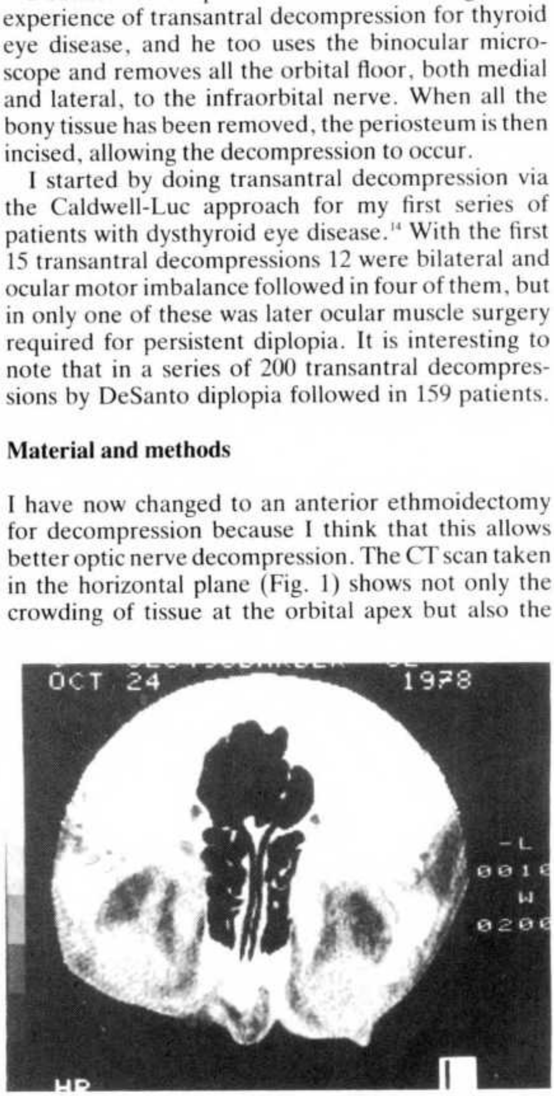

Fig. 1 *CT scan in horizontal plane of patient with bilateral, severe dysthyroid eye disease. The enlarged muscles are causing optic nerve compression at the orbital apex, particularly on the left side. The left medial rectus muscle is also bulging the ethmoidal wall medially, that is, attempting autodecompression.*

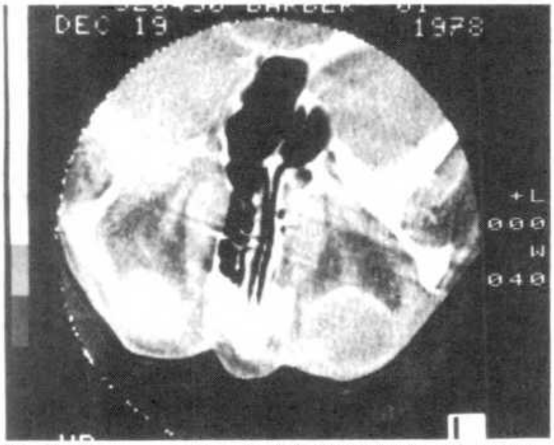

Fig. 2 *The same patient after left ethmoidal decompression. Note the medial rectus displacement into the ethmoids and the extra space at the orbital apex. Compare with the unoperated right side.*

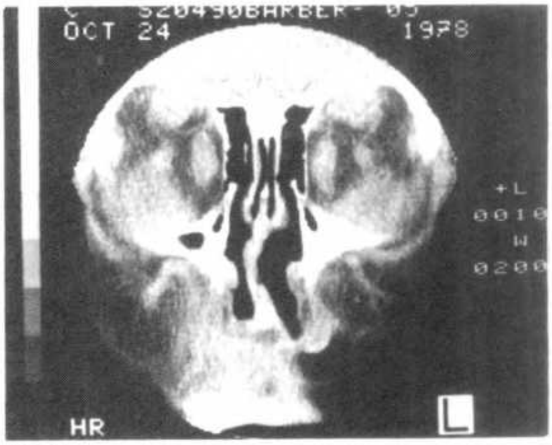

Fig. 3a

Figs. 3 (a) *and* (b) *The same patient shown in the coronal plane* (a) *before, and* (b) *after left ethmoidal decompression.*

inward bowing of the lateral walls of the ethmoidal sinuses. This is really the beginning of autodecompression. The volume of the ethmoidal space is usually larger than that of the antrum in most Caucasians and it would seem that the most important part of the decompression may best be achieved via the medial wall. I carry out this operation with my ear, nose, and throat colleague, Mr B H Pickard, who makes a skin incision high on the side of the nose and then strips the periosteum and the orbital contents laterally before clearing the ethmoidal cells away, going up as high as the cribriform plate and then moving across to take the medial half of the orbital floor. I rarely ask him to try to go across the whole of the orbital floor, but occasionally it is necessary to unroof the infraorbital nerve and move across lateral to the orbital nerve when maximum decompression is essential. My ENT colleague's reluctance to carry out this ethmoidectomy as a simultaneous bilateral procedure has been overcome since he has never yet had any signs of ischaemia of the tip of the nose, which he thought initially was a real risk. Once the bony space has been created I incise the periosteum from posterior to anterior above the upper border of the medial rectus, below the medial rectus, and again in the inferiomedial part of the orbit parallel to the medial side of the inferior rectus. These three longitudinal incisions then have openings with lacrimal sac scissors in the coronal plane to make H-shaped flaps to allow maximum herniation of orbital fat (Figs. 2, 3).

Results

It has been apparent that adequate decompression is obtained by this means, with an average 4 mm of decompression being achieved on each side. What is of great interest to me is that, out of 14 patients who had such anterior ethmoidal decompressions, 11 had changes in their ocular movements.[15] In eight of them there was an A pattern of esotropia, one of them had an A pattern of exotropia, and two had esotropia. In some of these patients the esotropia was only temporary, but in many of them it persisted, and later ocular muscle surgery was required to restore binocular single vision.

Discussion

It is interesting to speculate on the probable causes of this very consistent pattern in the alteration of ocular

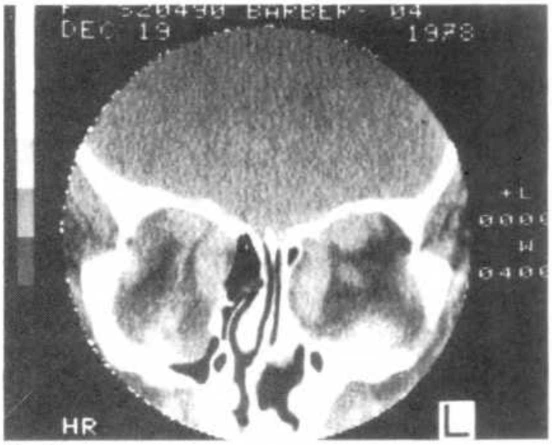

Fig. 3b

movements by the anterior ethmoidal decompression. I think that the explanation lies in our newly acquired knowledge of orbital fascial anatomy provided by Koornneef. The connective tissue septa from the upper and lower edges of the medial rectus muscle to the roof and floor of the orbit are displaced by the increased orbital fat and are incised when the longitudinal periosteal incisions are made. At the same time the orbital tension is released and the globe is pulled back into the orbit, but the increased mechanical advantage allowed to the medial rectus produces the esotropia. Because the longitudinal incision by the inferior rectus is only on its medial side and not on the lateral side of that muscle, the persisting connections of the orbital fascia on the lateral side of the inferior rectus do not allow the lower part of the globe to be pulled into such an esotropic position, and hence have a tendency to an A pattern. The increase in esotropia following surgery allows for an enhanced vertical action of the superior oblique, and this again produces an A pattern to the movements.

The reasons for orbital decompression have altered somewhat over the years. Initially they were only ever carried out for patients with sight threatening disease. Other indications in some surgeons' hands include decompression as a preliminary to ocular muscle surgery when there are more than 25 mm of proptosis bilaterally, which would in fact be further increased if ocular muscle recessions were carried out to improve the diplopia.[13] Some patients who cannot tolerate prolonged therapy with high dose prednisolone may also elect for orbital decompression to enable them to stop taking prednisolone. Younger patients in whom the proptosis has been of gradual onset and who may have quite white eyes without chemosis or conjunctival injection, but yet have marked bilateral proptosis with very wide palpebral fissures, are greatly handicapped by their appearance and request cosmetic surgery. Surgeons with wide experience in orbital decompression are now prepared to offer the treatment to such patients, though later ocular muscle surgery and lid surgery to deal with lid retraction may be required.

In more recent times Tessier's surgical approach to the frontal facial skeleton has been used by some surgeons for orbital decompression. The frontal skin flap is stripped down from the scalp bilaterally to expose the whole of the front of each orbit. The periorbita can then be freed on all sides of each orbit, and the relieving incisions into the periosteum may then be placed in all four quadrants of the globe in between where the rectus muscles run. Koornneef has used this approach, and his personal communication suggests that he is not having any significant alteration in ocular muscle balance by this procedure. This is presumably because there is a symmetrical and therefore more nearly equal alteration in all quadrants without a tendency to produce a bias towards A pattern of esotropia. This operation takes longer but may prove to be the best.

Conclusion

I should like to express my personal thanks to Professor Barrie Jones for his inspiration to me during my training at Moorfields Eye Hospital and subsequently as a member of his Professorial Unit team. I am indebted to him for his emphasis on anatomical understanding before devising surgical approaches to deal with particular problems, but beyond that I shall always be grateful to him for his teaching on the approach to the patient as a person and not merely as a case of some interesting condition. Our present lack of any adequate means to prevent ocular involvement in thyroid eye disease, which has such a very prolonged and distressing natural history over years, means that these essential old-fashioned attributes of the doctor have to be exercised to their fullest extent in the management of these unfortunate patients.

The beautiful CT scans are by courtesy of Dr Glyn Lloyd, of Moorfields Eye Hospital.

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Effect of age on visual acuity after cataract extraction

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SUMMARY The best Snellen visual acuity in the three months after cataract extraction was found to decline with the age of the patient. The relationship was identical in 111 patients who had extracapsular extraction and a Pearce tripod posterior chamber intraocular lens and in 50 patients who had intracapsular extraction with spectacle correction. Vision after operation varied from a mean value of 6/5 at 50 years to 6/12 at 90 years, a decline of 1 line per 13·4 years. In the intracapsular group, over a mean follow-up period of 14 years, the rate of fall in acuity with increasing age after operation was found to be statistically similar to that of the early postoperative acuity plotted against age for both types of operation. This suggests that the rate of decline with age is unchanged after a prolonged period of aphakia with presumed increased exposure to ultraviolet and blue light. The data were found to be similar to the decline in the neurosensory elements of vision with age measured experimentally in 20 phakic subjects by laser interferometry. This method of assessment of contrast sensitivity threshold effectively bypasses changes in the optical media. The findings indicate that the previously recognised drop in visual acuity with age is not related to changes in the aging crystalline lens and support the view that there is a decline in the neurosensory elements of vision. It is important to recognise this deterioration so that results of surgery or other treatment are adjusted to allow for the age of the patients.

The reduction in visual acuity in the healthy human eye after the age of 45 years was reviewed by Weale in 1975.[1] The same aging phenomenon may be detected by measuring contrast sensitivity function at high spatial frequencies.[2 3] Senile miosis seems to have too small an effect on retinal illumination to make any real contribution to the observed reduction in vision. Increased optical density and light scattering in the aging crystalline lens may be important, though a model designed to simulate cataract suggests this may not be a major factor,[4] and Weale[5] could not demonstrate any loss of transparency in human postmortem lenses with age.

Neurosensory changes with advancing years are probably more important. Morrison and McGrath[6] have used laser interferometry to assess the 'non-optical' components of vision in normal subjects. This method provides retinal stimulation independent of changes in the optical media, and the results suggest that deterioration with age is a function of changes in the neurosensory elements of vision. Indeed, significant neuron loss in the aging human visual cortex has been confirmed by Devaney and Johnson.[7]

Our study examines the age related changes in visual acuity after surgical removal of the crystalline lens. The aim is not only to verify that the aging lens is not an important factor in the reduction of vision with increasing age but also to establish a reference base line of visual acuity over the age of 50 years. At present publications quoting visual results of surgery or other treatments make no allowance for age and may therefore be neglecting an important variable.

Patients and methods

Two groups of patients were chosen:

Group A comprised one eye of each of 111 patients who had had uncomplicated extracapsular lens extraction with implantation of a Rayner-Pearce tripod posterior chamber lens. The operations were performed with the aid of an operating microscope with coaxial illumination. Patients with other ocular or systemic diagnoses which might have affected the visual acuity were excluded. Macular degeneration, amblyopia, diabetes, and corneal or vitreous

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opacities were the most common reason for exclusion. All cases had intact posterior capsules and none subsequently required secondary capsulotomy. In this series the rate of posterior capsulotomy has been less than 0·5% at four years. The mean age of the group was 68 years, range 41 to 89 years.

Group B consisted of one eye of each of 50 patients who had undergone uncomplicated intracapsular cataract extraction between 10 and 23 years previously (mean 14 years). The operations were performed without an operating microscope, and optical correction was by spectacle lenses. Cases excluded from the study were as listed for group A. In group B the mean age at operation was 62 years and the range 51 to 70 years. The mean age at final follow-up was 76 years, range 71 to 89 years.

The relationship between age at operation and the best Snellen visual acuity recorded in the three months following operation was analysed in both groups. In group B the visual acuity and age at final follow-up was also recorded, so that for each patient the final acuity could be compared with the acuity in the early postoperative period.

In a further analysis the slope of reduction in Snellen acuity with age as obtained above in the pseudophakic and aphakic groups was compared with the slope of the 'non-optical' and presumed neurosensory reduction of vision as measured by contrast sensitivity threshold using laser interferometry in healthy phakic eyes (data reworked from Morrison and McGrath[6]). These experimental contrast sensitivity data were measured at 40% contrast, whereas the clinical Snellen test type presents an uncertain contrast, probably in the region of 70%. To make the two sets of data more comparable it was therefore necessary to adjust the comparative scale of cycles/degree to Snellen acuity so that the mean values of the two groups coincided. The age profile of the experimental group was similar to that in the clinical groups A and B (mean 67 years, range 53 to 86 years).

To facilitate the statistical analyses Snellen acuities were transformed according to a simple linear code with a unit inverval of one half of a Snellen line and increasing with improving acuity; an acuity of 6/18 became 1 unit, 6/12 became 3, 6/9 became 5 units and so on. Linear regressions were performed to describe the variation of acuity code with age, and all regression line equations given in the text are expressed in terms of these transformed acuity codes. Product moment correlation coefficients were also calculated. The slopes of regression lines were compared by evaluating the appropriate *t* statistic from the regression data. A two-tailed sign test, a paired, nonparametric procedure, was used to examine the changes in acuity of group B over their follow-up period. These calculations were performed with the aid of the MINITAB package on the University of Glasgow ICL 2988 computer system.

Results

Fig. 1 displays the age related reduction of Snellen acuity (mean ±1 SD) measured in the early postoperative period. Visual acuity dropped from about 6/5 at 50 years to 6/12 at 90 years. The relationship of age to visual acuity was statistically significant for both groups at $p<0{\cdot}001$. The regression line for the extracapsular pseudophakia results, group A (acuity $=15{\cdot}1-0{\cdot}145\times$age; correlation coefficient$=-0{\cdot}740$; DF=109) was not significantly different ($0{\cdot}1<p<0{\cdot}2$) from that of the intracapsular spectacle aphakia patients, group B (acuity$=19{\cdot}0-0{\cdot}200\times$age; correlation coefficient$=-0{\cdot}638$; DF=48). A similar analysis could not detect any significant difference between males and females for either group ($0{\cdot}1<p<0{\cdot}2$).

Examination of the data on change in visual acuity within group B over the follow-up period (mean 14 years) showed the same gradient of deterioration with advancing years (Fig. 2). While there was a significant ($p<0{\cdot}001$) drop in acuity over the follow-up period, the regression line for the early postoperative results (acuity$=19{\cdot}0-0{\cdot}200\times$age, as above) was not significantly different ($0{\cdot}1<p<0{\cdot}2$) from that of the visual acuity at final follow-up (acuity$=12{\cdot}7-0{\cdot}106\times$age; correlation coefficient$=-0{\cdot}267$; DF=48). Males did not differ from females in this analysis ($0{\cdot}2<p<0{\cdot}5$). There was, however, a much wider scatter of the data in the follow-up recordings, reflected in the poorer correlation coefficient. We

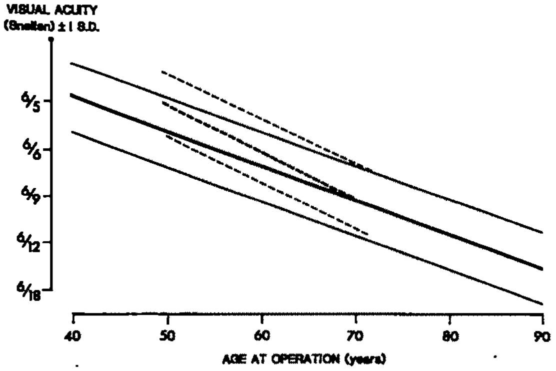

Fig. 1 *Regression lines (±1 standard deviation) showing the decline with age of best Snellen visual acuity measured in the first three months after cataract extraction. Solid lines represent extracapsular surgery with intraocular lens and dotted lines intracapsular surgery with spectacle correction. The two groups are not statistically different.*

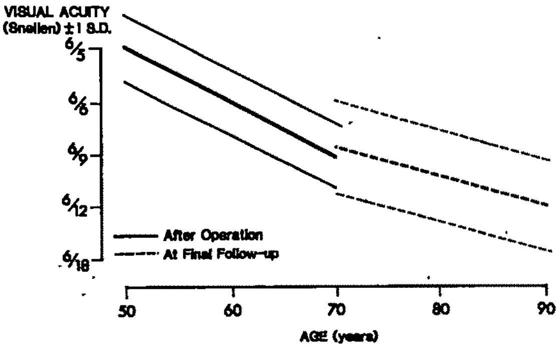

Fig. 2 *Visual acuity of group B in the three months after operation (solid lines) and after average follow up of 14 years (dotted lines) plotted against age. Statistical analysis suggests that the rate of decline with age is not altered by the period of aphakia.*

therefore sought to verify the observation by comparing the slope of visual acuity at final follow-up in group B (age range 71 to 89 years) with an age matched population selected from group A. This confirmed that there was no significant difference ($0·2<p<0·5$).

In Fig. 3 the slope of threshold frequency for laser interference fringes against age in the experimental study of 20 subjects is compared with the slope of postoperative visual acuity against age at operation in groups A and B combined. The reduction in spatial frequency discrimination in the experimental group showed a trend which was similar to that for Snellen acuity in the clinical groups. However, they were not identical. Statistical analysis showed the slopes to be significantly different ($0·01<p<0·02$).

Discussion

The results indicate that the best corrected Snellen visual acuity after cataract extraction declines with the age of the patient by 1 line per 13·4 years from 6/5 at 50 years to 6/12 at 90 years. Thus one would expect an average acuity of 6/6 at 63 years and 6/9 at 77 years. The relationship of visual acuity to age is identical in contemporary extracapsular extractions with posterior chamber intraocular lenses and in retrospective observations in intracapsular operations with spectacle correction. These different surgical techniques might have age related subclinical complications causing minor changes in acuity, but, as the two main potential complications, capsule opacification in extracapsular operations and macular oedema in intracapsular operations, are confined to each individual group, it is unlikely they would influence the results to an identical degree. In the analyses of visual acuity in the early postoperative period (Fig. 1) we assume that the decline with age has occurred before operation. This figure is very similar to Weale's display[8] of the slope of decline of visual acuity as a function of age in healthy phakic subjects. It also confirms the suggestion made by Owsley *et al.*[9] that for tests of contrast sensitivity at the higher spatial frequencies up to 18·2 cycles/degree there is no difference between older healthy phakic eyes and those in which an acrylic intraocular lens has replaced the crystalline lens.

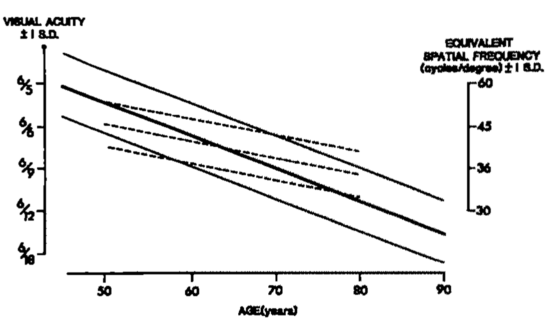

Fig. 3 *Combined data of groups A and B (solid lines) show a similar reduction of Snellen visual acuity with age to the reduction of threshold frequency for laser interference fringes with age (dotted lines), from Morrison and McGrath.*[6]

It therefore appears that the deterioration in vision is not related to changes in the crystalline lens. Furthermore the same relationship is confirmed when the change in visual acuity is examined after a long period of aphakia (Fig. 2), so that, in the absence of identifiable disease, the condition of aphakia neither accelerates nor retards the deterioration of visual acuity with advancing years. This is an interesting observation in view of the current interest in phototoxic retinal effects of ultraviolet and blue light.[10-13]

We have treated the data on the assumption that the trend is part of a linear function, and this may be a crude though justifiable approximation. The wider scatter of data in the follow-up observations in Fig. 2 may conceal an alteration in the gradient of reduction in vision in the very old patients. We would also expect the slope to be flatter towards the younger end, as previous data[1] suggest that only over 45 years of age is there a fall off in visual acuity. We have insufficient data at the extreme ends of the age range to examine these possibilities.

Our findings in pseudophakic and aphakic patients are similar to those of the experimental assessment of non-optical components of vision in the study by Morrison and McGarth.[6] This again suggests that the reduction in vision with advancing years is not a function of changes in the crystalline lens but a result of degenerative changes in the neurosensory components of vision. The lines shown in Fig. 3 are not identical, but they represent radically different test systems with different effects on wide angle light scatter and chromatic aberration. Therefore the slightly different gradients could still represent the same phenomenon. In addition the small number of observations in the laser interference group limits the scope for statistical comparison.

Whatever the theoretical considerations, it is important in assessing clinical results after cataract surgery or indeed after any form of therapy, that the visual acuity is adjusted to allow for the decline in visual acuity with age.

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Public health ophthalmology

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SUMMARY Public health ophthalmology, often referred to as preventive or community ophthalmology, focuses on three community based activities: preventive, curative, and promotive. The pioneering work of Professor Barrie Jones in this field is recognised. Examples of each activity are provided, with emphasis on the developing world.

Professor Barrie Jones can be considered one of the pioneers in the field of public health ophthalmology, with particular emphasis on the integration of eye care into the health care delivery systems in the countries of the developing world. His blending of research activities both in the laboratory and in the field with the excellent public health ophthalmology course in the Department of Preventive Ophthalmology in London has resulted in a career replete with scientific achievements as well as training a new generation of participants dedicated to carrying on his work in many parts of the world.

I found it most interesting to review his bibliography, which revealed a broad spectrum of interests ranging from longstanding activity in research dealing with chlamydial infections in general and trachoma in particular, corneal graft surgery, the aetiology and chemotheraphy of herpes simplex infection, and pharmacological studies of antiviral and antionchocerciasis drugs; to name only a few. But I was most impressed with his abiding and continuing interest in veterinary medicine appearing in the *New Zealand Veterinary Journal* and other similar publications dealing with such diverse subjects as idiopathic, familial hyperchylomicronaemia in a cat, adamantinoma in a cat, feline leukaemia virus testing, a collagen dysplasia in a greyhound bitch, gastric carcinoma in a bitch, and myotonia in related chow chow dogs. This broad spectrum of interests demonstrates not only his research virtuosity but also a commitment to report interesting and important research observations whenever and wherever they may occur.

Preventive, or community, or public health ophthalmology has only recently begun to attract attention in the ophthalmological world. There are three activities that constitute this approach to the delivery of eye care, namely, preventive, curative, and promotive activities.

Prevention of disease

Preventive activities rely heavily on research, not only performed in the laboratory but also carried out in the community by epidemiological techniques to identify high risk populations for specific diseases. The cohort studies conducted in Framingham, Massachusetts, helped to establish smoking, systemic hypertension, overweight, and lack of physical exercise as risk factors for the development of coronary heart disease. The numerous case control studies in both Great Britain and the United States established cigarette smoking as the major risk factor for lung cancer. To perform these studies we must leave our office and proceed to the community to design the study, recruit the participants, and conduct the examinations. In the developing world, especially South-east Asia, risk factor assessment in preventing the increasing morbidity and mortality from blinding malnutrition secondary to vitamin A deficiency has pointed to infant diarrhoea, measles infection, and borderline liver stores of vitamin A as probable risk factors. In each case prompt and adequate administration of vitamin A—in oral rehydration fluids in the case of diarrhoea or by mouth in oil suspension—can protect the child from developing clinical signs and symptoms of xerophthalmia and keratomalacia. By identifying those populations at highest risk, the distribution of vitamin A can be targeted primarily to those children in greatest need of it.

A second example of preventive activity deals with identifying those individuals in populations at greatest risk for developing angle-closure glaucoma. We know that in China, and countries to the south

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including Laos, Vietnam, Cambodia, and extending to Burma, angle-closure glaucoma is much more prevalent than open-angle glaucoma. In fact it has been estimated that 50–90% of all glaucoma in these areas is of the angle-closure type. Thus a screening outreach programme to identify those individuals over the age of 35 years whose anterior chamber depth is 1·7 mm or less would identify such a high risk population. If such a population was followed up for five years and the incidence of angle-closure glaucoma attacks was 5% per year or more, then one could consider prophylactic iridotomy to prevent such an occurrence. There is now available a portable, battery operated YAG laser which could be used in the field to perform an iridotomy under topical anaesthesia. With such an outreach programme, especially in those countries where the major population still resides in rural communities, a serious cause of blindness and visual disability could be prevented.

Curative programmes

The second component of public health ophthalmology is curative. In the developing world, cataract is much the most prevalent cause of blindness and offers an excellent example of the curative aspects of public health ophthalmology by a well proved, safe, and effective surgical intervention. Such a curative programme can function most effectively if it combines an efficient screening programme to identify people blind from cataract, a strategy to make the surgery available and to motivate the patient to seek such treatment, and a facility whereby the surgical procedure and postoperative care can be provided. Where possible, such curative components should be integrated into the existing health care infrastructure, so that screening for cataract can be performed by primary health care personnel in villages and small towns and the surgery performed in rural districts or provincial hospitals with appropriate facilities and personnel. The great challenge facing our profession is to increase the efficiency of cataract surgery without decreasing its safety. In the developing world alone there are about 14 million blind from cataract and perhaps as many as five million new cases each year. Thus the total number of operations performed each year in the developing world must be trebled, from a present level of 2½ million to at least seven million both to keep up with new cases and to reduce the backlog of cataract blind. It is apparent from the formula below that, to increase the cases operated per year,

$$\text{Cases/year} = \frac{\text{number of beds} \times \text{days/bed available/year}}{\text{length of stay/days}}$$

one must either increase the number of beds, which is very expensive, increase the number of days that the beds are made available, which is already at a maximal number, or decrease the length of postoperative stay in hospital. At present the average length of stay is about five to six days. If this could be reduced to one or two days, a three-fold increase in capacity to perform cataract surgery would be possible. This increased capacity must be coupled with increased case finding and increased motivation on the part of the patient to seek surgery.

Education

The third component to be discussed is the promotive component. Educational material can provide simple ways of improving personal hygiene, advise on proper diet such as adding dark green leafy vegetables high in beta-carotene to the diet of young children, and increase awareness of the availability of surgery to restore sight to the cataract blind. Legislative action can be directed towards better safety conditions in mining operations or supporting training programmes for allied health personal, who play such an important part in delivering eye care within the whole health care system. Publicity directed towards shaping public opinion on reducing the prevalence of blindness can be as effective in changing the behaviour of individuals and achieving a 'health revolution' as it was in shaping the behaviour of farmers in India with respect to the 'green revolution'. All audiovisual techniques available can be harnessed to this end.

Finally increased co-operation and collaboration among the national committees of each country, the active non-governmental organisations that are sponsoring ongoing programmes, and the country representatives of the World Health Organisation will help mobilise needed resources and enhance political will for there to be a strong and effective prevention of blindness programme within the overall health care national programme. Only then, in the words of Professor Jones, will the 'burden of avoidable blindness' be removed once and for all time.

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The enigma of herpes stromal disease

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SUMMARY Herpes stromal disease is due to direct damage as a result of viral replication, virally induced immune mechanisms, or a combination of the two. Viral replication may have a major initiating role in the production of herpes simplex and herpes zoster induced stromal disease, and steroids may initially be harmful in their treatment. On topical antiviral drugs alone, in patients who never previously had had topical steroids, 14 of 15 cases of herpes simplex induced disciform keratitis responded favourably in an average of 44 days of treatment. This compared with one out of 14 responding if steroids had previously been used, 13 of 14 requiring topical steroids and an average 112 days' treatment. In herpes zoster stromal disease cases 78% had epithelial involvement, 54 of 57 responded to topical antivirals alone without the use of steroids, 2% recurred, and treatment averaged a total of 62 days. If steroids were used alone or in combination with antivirals, there was a 50% recurrence rate and 200 day total treatment duration.

Two sorts of herpetic infections affect the corneal stroma, namely those due to herpes simplex and those due to herpes zoster infection. Both conditions present peculiar and testing diagnostic or therapeutic problems in many cases, and both conditions are often difficult to treat, prone to recurrences leading to corneal scarring, progression of disease to other parts of the eye not initially affected, and much visual loss. It is uncertain whether stromal disease is caused by viral replication alone (leading to cytolysis), by virally induced immunological mechanisms, or a combination of both, and this uncertainty is reflected in the inadequacy of treatment of these conditions.

Traditionally both conditions have been treated with steroids, but treatment has been prolonged, with frequent recurrences, and it is sometimes difficult to wean a patient completely off low dose maintenance topical steroids. Often despite treatment the disease spreads to parts of the eye not initially affected.[1] Furthermore steroids, apart from being associated with local side effects, can lead to a continuation of the disease process by enhancing viral replication and suppressing local immune and defence mechanisms, and this could explain the chronicity of the disease.

The aim of this paper will be to present evidence that viral replication plays a major part in the disease process, and that early antiviral drug treatment of these two conditions has many advantages and is possible without the concomitant use of steroids.

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Herpes simplex stromal disease

Herpes simplex virus infection is common throughout the world and in the United Kingdom represents the commonest infectious cause of blindness, with 2·3% of all cases being notified to the central register.[2] Stromal disease occurs in 25% of patients after their first herpes simplex epithelial ulcer,[3 4] with 75% occurring within the first year. If topical steroids are used in the initial ulcerative attack, there is a higher incidence of stromal disease.[3 5] There are two sorts of stromal response, that underlying an active epithelial ulcer, and that occurring some time after the epithelial lesion has healed, or indeed occurring without a preceding epithelial lesion. In the latter case the typical stromal lesion of disciform keratitis is a centrally localised infiltration with oedema and swelling of the corneal stroma, folds in Descemet's membrane, and sometimes secondary glaucoma, uveitis, or occasionally an overlying dendritic ulcer. Alternatively the lesion may be eccentric or occupy the entire cornea. The exact classification, though, of the herpes simplex induced stromal diseases must await the determination of the exact and relative role of virus replication and immune mechanisms.

Herpes zoster stromal disease

Herpes zoster infections occur in 0·2% of the population, with the trigeminal nerve the most commonly involved. Of these cases ocular involvement occurs in

Table 1 *Herpes zoster keratouveitis: a retrospective analysis of 112 patients, of whom 82 had epithelial lesions, showing the incidence of stromal lesions and uveitis subsequently developing*

	Disciform keratitis		*Localised infiltrate*		*Uveitis*	
	No.	*%*	*No.*	*%*	*No.*	*%*
	23	20·5	31	27·6	81	72·3
With preceeding epithelial lesion (82)	18	78·3	24	77·4	77	95
No preceeding epithelial lesion (0)	5	21·7	7	22·6	4	5

over 50%. In the acute phase 50–73% will develop epithelial involvement, either a punctate keratopathy or pseudodendritic formation.[6,7] In a recent retrospective analysis of 112 patients 42 (37·5%) developed stromal disease after previous epithelial involvement as opposed to only 12 patients (10·7%) developing stromal disease with no preceding epithelial involvement. In other words, if there had been previous epithelial involvement, over 50% (42 out of 82) developed stromal disease (Table 1).

In the same analysis it was found that anterior stromal nummular infiltrates or passages were geographically related to previous epithelial disease in 92% of patients, occurring soon after the onset of epithelial disease itself. Disciform keratitis occurred in 20% of patients, and characteristically after a delayed interval—after more than 21 days—78% having had previous epithelial disease. Uveitis occurred in 72% of all patients, only 5% of whom had not had preceding epithelial disease. Late epithelial disease, including delayed mucous plaques associated with corneal anaesthesia and previous epithelial disease, and neuroparalytic and exposure keratitis, represents epithelial disturbance rather than active viral invasion, for no herpes zoster virus has been isolated from these lesions.

Corneal response to viral infection

When viral infection takes place, tear immunoproteins such as IgA and IgG act to neutralise the virus and prevent it colonising the epithelial cells. Once this has occurred, though, viral replication takes place within the cells, which are destroyed, an ulcer results, and free virus is released. Either virus penetrates the stroma, enters the keratocytes, replicates, and leads to cytolysis, which in itself leads to an acute inflammation, or soluble viral antigen permeates from the surface and becomes attached to the stromal keratocyte membranes, altering their membrane antigenicity and setting up an immune reaction. Finally, incomplete viral particles can enter the stroma, setting up an immune reaction. In herpes simplex stromal disease the local cellular or immune reaction is mainly T cell mediated, with sensitised lymphocytes producing cytotoxicity by way of a local cell mediated hypersensitivity. Natural killer T cells, whose action is not dependent on previous sensitisation, may also play a part, for they have been shown in graft rejection to destroy donor endothelial cells.[8] Thus the stromal response is due to soluble sensitised immunoprotein, such as IgG, acting together with a sensitised cell mediated system, with activation of complement. The HLA antigen system is expressed in the normal corneal stroma with both class I HLA antigens, the major histocompatability complex antigen acting as an effective agent for both cellular and humoral immune systems, and class II HLA systems present.[9] After herpes simplex infection HLA class II (HLA D) antigens are expressed on stromal cells (Ward K A, *et al.*, in preparation). Such abnormal expression of class II antigens is observed in a variety of autoimmune diseases and would explain how the HSV virus can initiate a cell mediated response.

Such humoral and cellular mediated responses would block viral replication, causing an abortive reaction, but as the virus has already entered the keratocyte its surface antigenicity would have been altered, so that the corneal defence mechanism would recognise it as 'non-self', producing a cell mediated response. It is a feature of both herpes simplex and zoster disciform keratitis that the disease process is chronic. If the reaction was simply due to a cell mediated hypersensitivity reaction, it would be expected to be self limiting, but with topical steroid treatment, either after or during withdrawal, rebound recurrences are frequent, suggesting continued antigenic stimulus. Nowadays, very few cases of herpes simplex stromal disease are left untreated with steroids, and much of the severity of these cases has been attributed to the advent of steroids,[10] which lead to local immunosuppression but allow viral replication to proceed with continued antigenic stimulation.

But what is the evidence that viral replication plays a part in the stromal response? In herpes simplex keratitis, tear herpes simplex virus (HSV) specific secretory IgA (sIgA) has been found after acute epithelial disease,[11] and there is a marked local production of virus specific IgG subclass in response to epithelial and stromal infection.[9] Antibody in this subclass may be poorly neutralising, as it fails to fix complement and only weakly promotes an antibody-dependent cell mediated cytotoxic reaction. Moreover IgG4 antibody production may result in an atopic reaction, as it combines with mast cells and causes degranulation when cross-linked by antigens, and this would account for some of the stromal destruction and response seen in stromal disease.

It was Barrie Jones who with Alan Patterson[12] showed that, if disciform keratitis was treated alone with steroids, a herpes simplex ulcer would appear on the epithelium in a high percentage of such cases. Herpes simplex particles have been demonstrated in the corneal stroma[13-17] and HSV isolated from organ cultured corneal discs in patients with disciform keratitis.[15 18] Herpes simplex viral particles have been seen in necrotising stromal keratitis.[13 19] Some workers have attributed disciform keratitis to a direct viral invasion of the endothelium on the basis of herpes simplex virus isolation from the aqueous,[20] and herpes simplex viral has been cultured from the aqueous in cases of focal iritis and persistent endotheliitis with a secondary glaucoma.[20] Incomplete virus, virions, or empty capsids have been found in the stroma of a patient with disciform keratitis, with HSV antigen localised either near herpes virions in keratocyte cell nuclei or in the stroma in areas of degenerating keratocytes[16-18] and on keratocyte nuclear membranes.[16]

The sources of such virus include the stroma itself, the ocular adnexa and tears, and the trigeminal ganglion known to be colonised after infection[21] reaching the stroma by way of the corneal branches—the so-called back door approach[22]. Such continued antigenic stimulation would suggest initiation by residual virus or viral remnants. The clinical appearance of disciform keratitis can be produced in the rabbit eye by herpes antigen injection,[23 24] antigen being found on the stromal keratocytes with lymphocytes in close proximity, suggesting a cell mediated response. The direct injection of herpes virus into the rabbit stroma produces infiltrates, though its similarity to the clinical picture of disciform keratitis is uncertain, and such an animal model is probably more akin to the infiltrate beneath an ulcer in man. Antiviral treatment of these infiltrates with either triflurothymidine[25] or bromovinyldeoxyuridine[26] improved the stromal response.

In rabbits different herpes simplex strains produce different responses. Strains producing a stromal response have an increased glycoprotein content compared with those producing only epithelial responses,[27] and there is evidence that genetics plays a part, for the viral genome determines the extent of ocular herpes infection, its severity, its tendency towards recurrent disease, and the tissue response to steroids, independently of any host immunity or resistance.[28] If the appropriate HSV strain is inoculated into the rabbit cornea, stromal involvement is seen beneath the ulcer, and a disciform keratitis lesion is seen after the seventh day.[28 29] But polymorphonuclear cells are important in the development of the lesion, for if the rabbits are treated with serum acting against the polymorphonuclear cells the reaction is much less.[30]

In herpes zoster infection the exact mechanism and pathogenesis of the ocular signs is not known, partly because of the paucity of pathology of the stromal lesions and partly owing to the lack of a suitable animal model. Herpes zoster virus has been cultured from the acute epithelial lesions of both punctate keratopathy and pseudodendrites,[31] from which multinuclear giant cells and intranuclear occlusion have been found[32] and which are the most common manifestation of ocular involvement. A high proportion (92%) of the anterior stromal deposits which resolve into nummular scars occur in areas underlying a previous punctate keratopathy or pseudodendritic ulcer[6] (Table 1). These lesions could be due to direct viral invasion, or the diffusion of soluble viral antigen into the stroma, or damage to the terminal corneal nerves from virus travelling down the trigeminal branch. Similarly keratouveitis frequently occurs after epithelial involvement—in 95% of patients[6] (Table 1). It is uncertain whether the ocular abnormalities are due to vasculitis causing ischaemia or chronic inflammation. Histological examination of early cases has shown that only the epithelium tends to be affected, with the deep corneal layers clear, but in chronically affected cases granulomatous reactions to Descemet's membrane have been seen,[33] and viral particles have been found in the endothelium[34 35] and retina.[36] Disciform keratitis also occurs after epithelial disease but not in the same area, and, as lymphocytes are found in the affected region, it is thought to be due to a hypersensitivity reaction to viral antigen.[6]

Thus the available evidence points to direct viral involvement of the stromal lesions in both herpes simplex and zoster disease, either by setting up a cytotoxic reaction after cellular invasion, or by initiating immunological mechanisms which are responsible for the clinical signs that are so familiar in these cases. If it could be shown that those antiviral agents which enter the stroma in therapeutic concentrations do control the disease process, this would be evidence that viral replication at least plays a part—an initiating role—in such disease processes.

Clinical results

TOPICAL ANTIVIRAL CHEMOTHERAPY

Herpes simplex disease

INTRODUCTION

Topically applied chemotherapeutic drugs have a definite role in the treatment of epithelial disease,

Table 2 *Outcome of comparative trial of topical acyclovir (ACV) and adenine arabinoside (Ara A) on the stromal response beneath herpes simplex epithelial lesion. Treatment was five times a day until the signs resolved, then it was weaned off over two weeks*

	Number	*Healed*	*Days to heal*	*Steroids required*
ACV	20	20	12·3	0
ARA-A	17	12	8·0	5

From McGill, Tormey, Walker.[37]

known to be due to viral replication and virally induced cell destruction, but do not affect either latency[3-5] (recurrences) or the incidence of subsequent stromal disease. Idoxuridine, which is highly insoluble and does not penetrate into the corneal stroma, has no effect on stromal disease, but the question arises whether alternative antivirals that do penetrate have such an effect.

CLINICAL

Patients were divided up into those who had a stromal response beneath an active corneal ulcer, and those who had a typical lesion of herpes simplex disciform keratitis following on a previous attack of dendritic ulceration but with no concurrent epithelial disease present. In a double blind trial topical acyclovir and adenine arabinoside were compared in the treatment of the herpes simplex stromal response beneath the ulcer. Acyclovir was superior to Ara-A[37] (Table 2).

In disciform keratitis acyclovir alone was of effect only in those patients who had never previously had topical steroids. Fourteen of 15 such patients responded satisfactorily, but if topical steroids had been used in a previous attack (with topical antivirals) then only one of 13 responded satisfactorily. The duration of treatment of acyclovir treated patients was shorter and rebound recurrences fewer than for those patients treated with a combination of acyclovir and steroids. In other words, once steroids were added to the regimen, all the familiar problems of steroid treatment, namely prolonged treatment therapy and frequent recurrences, were seen (Table 3). The degree of visual loss resulting from the residual stromal scarring was the same in the two groups, showing that withholding steroids did not lead to increased stromal scarring.

CONCLUSION

For those patients with their first attack of disciform keratitis and who have never been treated with steroids, topical antivirals that penetrate to the corneal stroma have in a comparatively short treatment course been successful in a high percentage of cases, without any significant sight impairing residual stromal scarring. The reason why prior steroid therapy makes the patient steroid dependent for subsequent attacks is unknown.

Adenine arabinoside is known not to penetrate the corneal stroma in therapeutic amounts. This explains why topical acyclovir was superior in treating herpes simplex induced infiltrative stromal disease beneath an ulcer. That topical acyclovir alone was able to control the stromal disease suggests that viral replication plays at least a part in the disease process. Collum and his colleagues[38] found that, in a comparison of acyclovir with or without topical steroids in the treatment of disciform keratitis, 40% of those patients treated with acyclovir alone healed within 50 days, but it is uncertain how many had had steroids previously, so that these results may have been improved if these patients had been excluded. Similarly Sanitato *et al.*[19] and Kaufman[39] found that acyclovir alone had a beneficial effect in five of 12 patients with disciform keratitis, but it was not clear from their results how many of these patients had had prior attacks treated with steroids. Acyclovir has also been successfully used in the treatment of presumed herpetic iridoxcyclitis when given either topically (personal observation) or systemically.[40]

It is suggested that for the first attack of herpes simplex induced stromal disease acyclovir or trifluoro-

Table 3 *Response of topical acyclovir (ACV) or triflurothymidine (F3T) on herpes simplex disciform keratitis in patients who either had never had topical steroids or had had a previous attack of stromal disease treated with steroids and antivirals*

	No.	*Healed*	*Signs resolved*	*Treatment duration (days)*	*Recurrences*	*Average follow-up (months)*	*Change in vision*		
							Percent same	*Loss 1 line Snellen*	*Loss >1 line Snellen*
No prior steroids									
ACV	15	14	16·5	44·3	1	43·2	67%	33%	
F3T	1	1	21	40	0	8			
Prior steroids									
ACV	13	1	16·7	112	7	48·6	53·8%	23·1%	23·1%

thymidine five times a day for two weeks should be initiated. If after this time there is no regression of the clinical signs, topical steroids should be added and, once the signs have regressed, the patient cautiously and slowly weaned off. As viral resistance to acyclovir has been seen both experimentally and clinically,[41 42] administration of the drug should be limited to as short a treatment period as clinically necessary.

HERPES ZOSTER INFECTION

If a drug has an effect on the skin rash which is known to be due to direct viral invasion, then, if zoster keratouveitis in its many forms is due at least in part to viral invasion and virally induced tissue damage, it would be expected that that drug would control some of the corneal disease.

The earlier available antivirals had no effect on the acute stages of the rash, or the incidence of postherpetic neuralgia, when given either systemically as adenine arabinoside[43] and cytosine arabinoside[43 44] or topically as idoxuridine, which initially, when combined with dimethyl sulphoxide (DMSO) for skin penetration, was thought to be of benefit[45] but later found to have no benefit over DMSO alone.[46] Systemic steroids used to lessen postherpetic neuralgia resulting from viral induced tissue damage carried the risk of virol dissemination.[47] Acyclovir has been shown in vitro to have antiviral activity against the varicella zoster virus,[48] and initial clinical trials suggested a beneficial clinical effect on the skin rash.[49] Placebo controlled double blind trials of intravenous acyclovir have shown that acyclovir treated patients fared significantly better in terms of duration of new lesion formation and the time of loss of vesicles and the time to full crusting.[50-52]

Intravenous therapy is not an ideal mode of therapy for most patients, and so an oral form of the drug has been developed. In a multicentred controlled clinical trial oral acyclovir at 800 mg five times daily for seven days has been found to be superior to placebo in significantly reducing the skin rash duration and associated pain (McKendrick *et al.*, in press), whilst Cobo *et al.*[53] have shown that oral acyclovir at 600 mg five times a day for 10 days, when compared with placebo in herpes zoster ophthalmicus, significantly reduced skin involvement and viral shedding, and ocular disease signs were lessened.

The question arises whether a drug effective against the skin rash is effective also against corneal disease.

CLINICAL

An open study of acyclovir ointment in acute herpes zoster keratouveitis showed that most patients had a quick resolution of their symptoms without any recurrence of the disease process.[54] This was in sharp contrast to the common clinical finding that patients treated with topical steroids required a prolonged course and suffered frequent recurrences. For this reason a double blind trial was set up to compare topical steroid and acyclovir ophthalmic ointment in the treatment of acute herpes zoster keratouveitis[55] (Table 4). The total treatment duration in the acyclovir treated group was considerably less than for the steroid treated group. In a short follow-up of less than one year, while 12 of the 19 steroid treated patients had a recurrence of their keratouveitis once treatment was either being tapered off or stopped, none of the acyclovir treated patients had a recurrence. Corneal epithelial disease resolved significantly faster than in the acyclovir group, but there was no significant difference in the resolution of stromal disease, uveitis, or scleritis in the two groups.

In an attempt to gain a broader impression of the usefulness of acyclovir in acute herpes zoster keratouveitis, a retrospective analysis was carried out of all patients with this disease presenting at the Southampton Eye Hospital over a two-year period and treated by a number of doctors.[56] Retrospective analyses are not ideal, and exact differences between groups for particular signs resolving may not be clear, but, when the clinical outcome of these patients treated with either topical acyclovir or steroids or a combination of both was reviewed, a definite pattern emerged. Topical acyclovir alone controlled the disease process in 51 out of 56 patients. Those treated with acyclovir fared significantly better, with a quicker resolution of their keratouveitis, as there were no recurrences of the disease process in the first year after treatment had been stopped compared with a 50% incidence of those treated with topical steroids, many of whom are still on treatment, so that the total treatment duration of the steroid treated patients was much longer.[56] With a longer follow-up two out of 56 of the patients treated with acyclovir had a recurrence of their keratouveitis, one of whom had had topical steroids for his lid involvement.[56] In an up-to-date retrospective analysis of all patients treated with topical acyclovir the time taken for resolution was the same for the different types of stromal disease (Table 5). But acyclovir, when combined with steroids, showed no benefit compared with the steroids alone. In other words the addition of steroids produces all the problems of prolonged treatment and frequent recurrences.

These trials, however, may have merely been showing the deleterious effect of steroids and not a beneficial one of acyclovir, as it was ethically impossible to use placebo controls in patients who had established keratouveitis causing a painful inflamed

Table 4 *Outcome of treatment with either topical acylovir or topical steroids (Betnesol) five times a day on acute herpes zoster ocular involvement*

Group	*Number*	*Number healed*	*Initial treatment duration (median days)*	*Number disease reappeared*	*Total treatment duration (median days)*
Acyclovir	17	16	75	0	75 (range 17–144)
Steroids	19	18	68	12* (63%)	280† (range 34–440)

*$p<0{\cdot}001$ (Fisher's exact test, 2-tailed).
†$p=0{\cdot}002$ (Mann-Whitney U test, 2-tailed).
From McGill and Chapman.[55]

Table 5 *Herpes zoster keratouveitis: retrospective analysis of patients treated with topical acyclovir compared with those treated with steroids or a combination of both*

Number	*Acyclovir (112)*			*Steroids (74)*			*Acyclovir + steroids (14)*		
	No.	*Healed*	*Days to heal*	*No.*	*Healed*	*Days to heal*	*No.*	*Healed*	*Days to heal*
Epithelial	82	82	6·06	20	20	10	4	4	12
Disciform keratitis	25	25	16·6	16	16	38	2	2	48
Nummular keratitis	32	29	15·4	19	19	27·7	3	3	61
Uveitis	89	83	21·7	56	56	53	7	7	92
Average treatment duration			62·3			200			197
Total recurrence rate			2%			50%			57%

eye. If in very early cases it could be shown that acyclovir stopped the disease from developing (compared with placebo), this would support the concept of an active role for this drug. In an attempt to settle this problem a prophylactic double blind placebo controlled trial was carried out on patients whose skin rash had resolved and whose eye showed minimal involvement of conjunctival injection or simply an acute punctate keratopathy (Table 6). Of the 20 patients treated 10 had topical acyclovir, 10 topical placebo. All patients treated with topical acyclovir fared well, with a quick resolution and no disease progression or stromal involvement. Eight out of 10 of the patients treated with placebo had a progression of their disease, with stromal involvement, and acyclovir had to be added before the disease resolved.

Table 6 *Outcome of a randomised double blind trial of topical acyclovir compared with placebo in the treatment of herpes zoster keratouveitis. The ocular signs at the onset were minimal, either being conjunctival injection or an early punctate keratopathy (early corneal involvement). The ocular disease process was halted in the acyclovir treated patients but progressed in 8–10 placebo treated patients, showing that acyclovir actively protects the eye from damage if treatment is started early enough*

Treatment	*No. of patients*	*Halted*	*Progressed*
Acyclovir	10	10	0
Placebo	10	2	8

Table 7 *Herpes zoster keratouveitis: In nine patients, showing the cause of failure to respond to topical acyclovir (several patients had more than one sign)*

	No.
Scleritis	3
Nummular infiltrate (2 had marginal infiltrate)	3
Uveitis	6

In reviewing all 112 acyclovir treated patients, all but one of whom presented within three weeks of the onset of their disease, we noted nine not responding to acyclovir alone (Table 7). It is suggested that if scleritis or uveitis persists, especially if synechiae have formed, steroids should not be withheld.

CONCLUSION

Most cases of herpes zoster stromal disease follow epithelial involvement, with nummular opacities occurring sooner than disciform keratitis, suggesting a different mechanism. As epithelial lesions are known to be associated with herpes zoster virus, and as stromal disease can be prevented if epithelial disease is treated with antiviral chemotherapy, and established stromal lesions can be similarly treated, this evidence suggests that viral replication has a major role in the development of these lesions.

Previously topical steroids were the only available treatment of herpes zoster keratouveitis, and they had to be continued for up to 18 months or more, with much disease progression, ocular damage and visual loss. With topical acyclovir there is a shorter treatment duration, less recurrence, and less disease spread, but it must be emphasised that this comparison may be showing up the deleterious effects of steroids on viral induced stromal disease, and further prophylactic oral and topically based clinical trials are required to determine the relative effective role of antivirals in this condition, particularly as the exact mechanism of the production of the different signs is not yet known. For instance, nummular opacities, which develop earlier than disciform keratitis and in direct relation to epithelial ulcers, may be due to a different immune mechanism than the cell mediated delayed immune mechanism of disciform keratitis.

General conclusion

In both herpes simplex and zoster ocular infections, stromal lesions usually follow after epithelial disease. The exact mechanism of these disease processes is not yet fully understood, partly owing to the lack of any suitable animal model. But the fact that stromal disease occurs after epithelial disease, and the effect shown here of antivirals on stromal disease, suggest that viral replication has a major role in the production of the stromal lesions. Antiviral treatment alone without the use of steroids offers considerable advantages, but the exact role of antivirals in the disease process must await further laboratory work and coded clinical trials. Prophylactic placebo controlled trials are required to determine whether topical antivirals are superior to placebo in all aspects of stromal disease, and whether any significant vision threatening stromal scarring results from the withholding of steroids.

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An outbreak of *Candida parapsilosis* endophthalmitis: analysis of strains by enzyme profile and antifungal susceptibility

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SUMMARY Twenty-two isolates from patients with postsurgical endophthalmitis due to infection with *Candida parapsilosis* as a result of exposure to a contaminated ocular irrigating solution were classified by enzyme profile analysis and antifungal susceptibility. These isolates were identical to a single isolate obtained from a contaminated vial but could be differentiated, on the basis of enzyme profile and antifungal susceptibility, from randomly selected stock isolates. The combination of these tests appears to have value in discriminating epidemic from non-epidemic strains.

The occurrence of a multicentred outbreak of postsurgical endophthalmitis due to *Candida parapsilosis* afforded an unusual opportunity to examine the characteristics of isolates obtained from patients at the various centres involved in the epidemic. The clinical outcome for many of these cases has already been described.[1] All of the patients had undergone cataract surgery in the course of which the anterior chamber of the eye was irrigated with a balanced salt solution (GBR, Lot No. 16738, Maury Biologicals, Los Angeles, CA).[2] An unopened vial of the solution bearing the same lot number was later found to be contaminated with *C. parapsilosis*.[2] In an attempt to confirm the common source of the infection, enzyme profiles and the antifungal susceptibilities of the isolates from patients, a vial of the solution, and the operating room environment, were examined and compared with a random selection of stock *C. parapsilosis* isolates.

Materials and methods

ISOLATE ACQUISITION

Candida parapsilosis isolates were recovered from patients with endophthalmitis by culture of fluid obtained by anterior chamber tap or vitreous aspiration.[1 2] None of the patients had been exposed to antifungal therapy prior to isolate recovery. The isolates on Sabouraud slants were mailed to our laboratory, where they were immediately subcultured on to freshly prepared Sabouraud's agar plates. Plugs from these plates were placed in sterile vials and frozen to −70°C for future use. An isolate of *C. parapsilosis* was recovered from an unopened vial of GBR solution (lot no. 16738). *Candida parapsilosis* was also isolated from the oxygen line used to ventilate patients during surgery at the first institution involved in the epidemic.[2] These isolates were handled in the same way as the human strains.

Eight *C. parapsilosis* isolates were randomly selected from the collection maintained at −70°C in the Microbiology Laboratory at Vanderbilt University Medical Center. Another nine isolates of the same organism were provided from stock maintained at Analytab Products (Plainview, NY). These isolates were also maintained on Sabouraud's agar at −70°C and were not passaged. Inocula for each of the following experiments were taken from these slants.

ENZYME PROFILE ANALYSIS

Enzyme profile analysis was performed by the API 20C clinical yeast system (Analytab Products). This commercially available system for the identification of yeasts from clinical specimens is composed of a series of miniaturised carbohydrate assimilation tests. The result is expressed numerically and is interpreted by reference to a computer generated data base of yeast strains.[3]

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ANTIFUNGAL SUSCEPTIBILITY TESTING

All isolates were evaluated in triplicate for their susceptibility to amphotericin B, ketoconazole, miconazole, and flucytosine.

Amphotericin B. The inoculum was prepared from cultures grown overnight on Sabouraud's agar and diluted in normal saline to give an 85% transmission on the B/L Spect 20 spectrophotometer at 550 nm (Bausch and Lomb). With the Microtiter System (Dynatech Laboratories, Inc.) serial two-fold dilutions of amphotericin B (Fungizone) were prepared in M3 medium to give final concentrations that ranged from 50 µg/ml to 0·05 µg/ml.[4] The plates were wrapped in aluminium foil with a wet sponge and were incubated at 32°C. To determine the minimum inhibitory concentration (MIC) the wells were read at 24 hours.

Flucytosine and the imidazoles. A similar technique was used for these compounds. The medium for determination of flucytosine (Roche Laboratories) susceptibility was yeast nitrogen broth supplemented with asparagine and dextrose. Casein yeast glucose agar in phosphate buffered saline was used for the imidazole studies (Janssen Pharmaceuticals).

Results

Twenty-three isolates of *Candida parapsilosis* were recovered from patients with postsurgical endophthalmitis. Twenty-two were available for testing. Ten of these were from California, four were from Florida, and eight were from Tennessee. All the California isolates came from a group of patients who underwent surgery at the same ambulatory facility. Two separate outpatient surgical centres were the source of the isolates from Florida (2,2), while three hospitals supplied the isolates from Tennessee (3,3,2).

Enzyme profile analysis. All the ocular isolates had the same API 20C enzyme profile (6756171) as the GBR solution isolate and the isolate from the oxygen tubing. Eleven of the 17 stock isolates also shared this profile.

Antifungal susceptibility. The antifungal susceptibility of the epidemic isolates to four antifungal agents is shown in Tables 1 and 2. Individual strains were considered to show a different response to an antifungal agent if the MICs differed by more than four-fold.

All the ocular isolates and the isolates obtained from the GBR solution and the oxygen tubing had the same pattern of susceptibility to each antifungal agent (Table 3). The antifungal susceptibilities of the

Table 1 *Epidemic isolates—San Francisco*

Strain	*Minimal inhibitory concentrations (MIC µg/ml) for 4 antifungal agents*			
	Amphotericin B	*Ketoconazole*	*Miconazole*	*Flucytosine*
1	0·625	0·1	1·56	0·2
2	0·312	0·1	1·56	0·2
3	0·312	0·1	1·56	0·2
4	1·25	0·1	1·56	0·2
5	0·312	0·1	1·56	0·2
6	0·312	0·1	1·56	0·2
7	1·25	0·1	1·56	0·2
8	0·312	0·1	1·56	0·2
9	0·312	0·1	1·56	0·2
10	0·312	0·1	1·56	0·2

Table 2 *Epidemic isolates—Florida, Tennessee*

Strain	*Minimal inhibitory concentrations (MIC µg/ml) for 4 antifungal agents*			
	Amphotericin B	*Ketoconazole*	*Miconazole*	*Flucytosine*
11Tn(1)	0·312	0·1	1·56	0·2
12Tn(1)	0·625	0·1	1·56	0·2
13Tn(1)	0·312	0·1	1·56	0·2
14Tn(2)	0·625	0·1	1·56	0·2
15Tn(2)	0·312	0·1	1·56	0·2
16Tn(2)	0·625	0·1	1·56	0·2
17Tn(3)	0·625	0·1	1·56	0·39
18Tn(3)	0·625	0·1	1·56	0·2
19Fl(1)	0·312	0·1	1·56	0·2
20Fl(1)	0·625	0·1	1·56	0·39
21Fl(2)	0·312	0·1	1·56	0·39
22Fl(2)	0·312	0·1	1·56	0·39

Tn=isolate from Tennessee.
Fl=isolate from Florida.

Table 3 Candida parapsilosis *Isolates (API 20C—6756171)*

Source	*Number of isolates*	In vitro *susceptibility to 4 antifungal agents (µg/ml)*			
		Amphotericin B	*Ketoconazole*	*Miconazole*	*Flucytosine*
Sf	10	0·312–1·25	0·1	1·56	0·2
Fl, Tn	12	0·312–0·625	0·1	0·78–1·56	0·2–0·39
GBR	1	0·625	0·1	1·56	0·2
OL	1	0·312	0·1	1·56	0·2
Stock	11	0·312–0·625	<0·05–>50	3·12–>50	0·1–25

Sf=San Francisco. Fl=Florida. Tn=Tennessee. GBR=Isolate from irrigation solution. OL=Oxygen line isolate.

Table 4 *Stock isolates*

Strain	*Minimal inhibitory concentration for antifungal agents (MIC μg/m)*				*API 20C Profile*
	Amphotericin B	*Ketoconazole*	*Miconazole*	*Flucytosine*	
A	0·625	0·1	3·12	12·5	6756171
B	0·312	0·2	12·5	25	6756171
C	0·625	0·2	6·25	12·5	6756171
D	0·625	25	>50	0·2	6756171
E	0·625	25	6·25	0·2	6756171
F	0·625	<0·05	6·25	0·2	6756171
G	0·625	12·5	6·25	0·2	6756171
H	0·625	25	12·5	0·2	6756171
J	0·625	<0·05	3·12	0·2	6756171
K	0·625	<0·05	3·12	0·1	6756171
L	0·625	>50	3·12	0·1	6756171
M	0·625	<0·05	1·56	0·2	6756173
N	0·625	0·39	>50	1·56	6756173
O	0·625	25	6·25	0·39	6756131
P	0·625	>50	1·56	0·39	6756131
Q	0·625	>50	12·5	0·1	6756131
R	0·625	0·1	1·56	0·1	6756131

17 stock isolates are listed in Table 4. The 11 isolates with the same API 20C profile as the ocular isolates differed from the ocular isolates in their susceptibility to at least one antifungal agent (Table 5). Five of the six isolates with different enzyme profiles also differed from the ocular isolates in their susceptibility to at least one agent.

Discussion

An epidemic of fungal infection is an unusual event. In most instances epidemiological techniques are used to identify the source of infection, and conclusive mycological evidence linking infected cases with a common source is seldom available.[5,6] During a recent investigation of an outbreak of candidiasis in a special care baby unit Phelps *et al.* used a resistogram typing method to determine the cause of the cross infection.[7] Others have suggested differentiating strains by the killer system.[8] But at present in contrast to bacterial infections, there are no techniques equivalent to phage typing that serve to identify specific fungal isolates.

Traditional methods of yeast identification that utilise carbohydrate fermentations and assimilations are complex and time consuming.[3,9] These methods have now been modified to provide a more practical approach to the problem.[3,10,11] The API 20C system we used is one such modification. It is a rapid and convenient method for identifying clinical yeast isolates. Classification of individual strains is based on the results of a series of carbohydrate assimilation tests. The seven-digit number expressing the result establishes an enzyme profile that serves to identify the strain by reference to a large data bank of previously analysed strains. Six different profiles have been identified for *Candida parapsilosis* (Levy I, personal communication, 1986).

Table 5 *Differentiation of 11 randomly selected isolates (API 20C—6756171) from epidemic isolates by MIC (μg/ml)*

Range of differentiation	*Number of isolates differentiated*	*Cumulative number of differential strains*
Amphotericin B		
<0·075–>1·25	0	0
Ketoconazole		
<0·05–>0·39	8	8
Miconazole		
<0·39–>6·25	7	10
Flucytosine		
<0·05–>0·39	3	11

In this study it was our purpose to determine whether the combination of enzyme profile analysis and antifungal susceptibility testing could serve as a useful epidemiological tool by separating epidemic from non-epidemic strains. All the ocular isolates had the same profile number (6756171) as the isolates recovered from the GBR solution and the oxygen line. However, this is a common profile for *C. parapsilosis*, being exhibited by up to 50% of isolates (Pincus D, personal communication, 1985). In fact this was the profile for 11 of the 17 randomly selected isolates. Thus the finding of a shared API 20C profile was not enough to link these isolates to each other or to the contaminated solution.

Antifungal susceptibility to the four antifungal agents was remarkably uniform for the strains involved in the epidemic. Although differences were noted with some strains, they were within the range of error of the test. The pattern was in contrast to that observed among the stock isolates with the same enzyme profile, each of which differed from the epidemic strains in susceptibility to at least one antifungal agent. Only with amphotericin B was the response uniformly similar. Five of the six isolates with different API 20C profiles also differed in their susceptibility to at least one antifungal agent.

These results suggest that the combination of enzyme profile analysis and antifungal susceptibility has some potential as a means of separating epidemic from non-epidemic strains. Whether any relationship exists between these two tests is unknown at this stage.

The API-20C enzyme analysis is based on the ability of the organism to utilise certain compounds as a sole carbon source, and this ability is genetically determined. Extended testing to additional compounds was not performed in this study but might have revealed differences between these strains. In this outbreak the actual cause of the intrinsic contamination of the irrigating solution was not determined, but it did occur at some stage during the preparation and bottling of the solution. While it is presumed that a single strain was responsible for the contamination, several strains with differences not detected by us may have been involved. Experience with the colonisation patterns in a special care baby unit, a somewhat parallel situation, suggests that this is certainly possible.[7] The origin of the isolate in the oxygen line is also not known with certainty at this stage, though it is likely to be related to the contaminating strain. The oxygen line was probably colonised during the period when the patients were exposed to the contaminating solution. Further studies with extended biochemical analyses of these and additional strains from other contaminated vials are needed to answer some of these questions.

From another point of view the uniformity in the response by all these epidemic strains to this wide battery of tests is remarkable in view of the broad geographic distribution of the cases and the differing periods of human passage prior to isolation.[2]

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Congenital hereditary corneal oedema of Maumenee: its clinical features, management, and pathology

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SUMMARY The clinical and histological features of congenital hereditary corneal oedema in 23 patients are presented. The series includes cases of both recessive and dominant inheritance. Although the condition is present at birth or in early childhood, visual development appears to be little impaired, if at all. Penetrating keratoplasty carries a relatively good surgical prognosis and can produce a substantial visual gain even when carried out late in life.

Congenital corneal opacities have been recognised since last century. Several underlying abnormalities have been described, including sclerocornea, Peters' anomaly, and congenital corneal clouding. This latter, congenital hereditary corneal dystrophy, had been described in the European ophthalmic literature,[1-7] but it was not until Maumenee's[8] report that the primary pathology was recognised as an anomalous development of the corneal endothelium. Since that time a number of further reports have appeared, mostly as individual cases[9-13] but also in the form of small series.[14-18] It is clear that there has been duplication of material between several of these publications. Recent reports have concentrated on description of the ultrastructural abnormalities in this condition. Judisch and Maumenee[18] made an attempt to differentiate the clinical behaviour of the oedematous corneas on the basis of dominant or recessive inheritance, but without regard for the ultrastructural details in either case.

The prognosis for useful vision in patients with congenital hereditary corneal oedema is still said to be poor, and penetrating keratoplasty is likewise thought to carry a poor prognosis of graft survival.[19]

In an effort to document the clinical manifestations of this condition and to elucidate useful prognostic factors as to maintenance of visual function and likely outcome of penetrating keratoplasty we report a series of 23 patients presenting to the surgeons of the Corneal Clinic at Moorfields Eye Hospital during the period 1971–86.

Materials and methods

Cases of congenital endothelial dystrophy were identified retrospectively from the cases notes of patients attending the Corneal Clinic, Moorfields Eye Hospital. All patients have been under the care

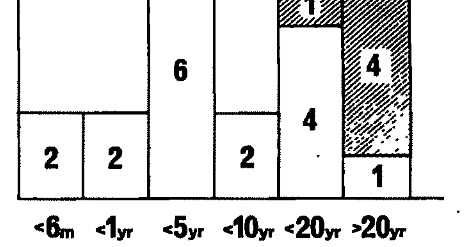

Fig. 1 *Age at presentation. The cross-hatched portions of the histograms in Figs. 1, 2, and 7 represent those patients with the dominant inheritance pattern.*

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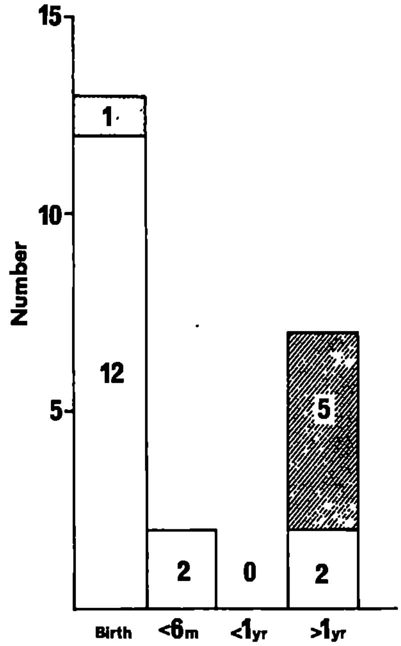

Fig. 2 *Age at onset of symptoms or signs. In one case it was not known when in childhood the signs first appeared.*

of at least one of the authors personally. The diagnosis of congenital hereditary corneal oedema was made on the basis of clinically recognisable, bilateral, corneal oedema developing in early life, and in the absence of any other anterior segment abnormality. Twenty-three affected individuals were identified, presenting between the ages of 3 months and 61 years, mean 13·5 years (Fig. 1). Corneal clouding had been observed in these patients from birth to as late as 8 years (Fig. 2). There were 15 males and 8 females.

One family was observed whose inheritance pattern was clearly autosomal dominant, and here the sex distribution of those seen was one male to five females, and 6:19 overall (Fig. 3, Figs. 4A, B, C). The remaining patients had either an autosomal recessive pattern (eight patients) or probable recessive pattern (nine patients). Fifteen patients were British, five Iranian, three Saudi Arabian, and one was Pakistani (Figs. 5A, B).

Progression of the corneal signs—that is, increase in oedema, development of corneal stromal scarring, and deposition of opaque plaques—was observed in four of the recessives and three of the dominants (Fig. 6). Vascularisation was clinically apparent in two patients over 50 years of age. Spheroidal keratopathy was seen in three of the dominants who were over 30 years of age and a similar change was seen in one 24-year-old recessive from Iran. One recessive case showed a temporary regression of the signs but at no time did he achieve normal visual acuities. No patient had any other anterior segment, developmental abnormality.

Five patients had undergone glaucoma surgery elsewhere, one in adulthood, the others in infancy (Table 1). In three patients, including one dominant, there was manifest nystagmus, and one had latent nystagmus. Strabismus was seen in four patients; one had an esotropia, two had an exotropia, and one an exophoria. No patient had both a squint and nystagmus.

One further case, a child aged 7 years, developed an exodeviation following his first graft, but this recovered after the second eye received a graft with evidence of good retained binocular function. No patient had any associated systemic abnormality.

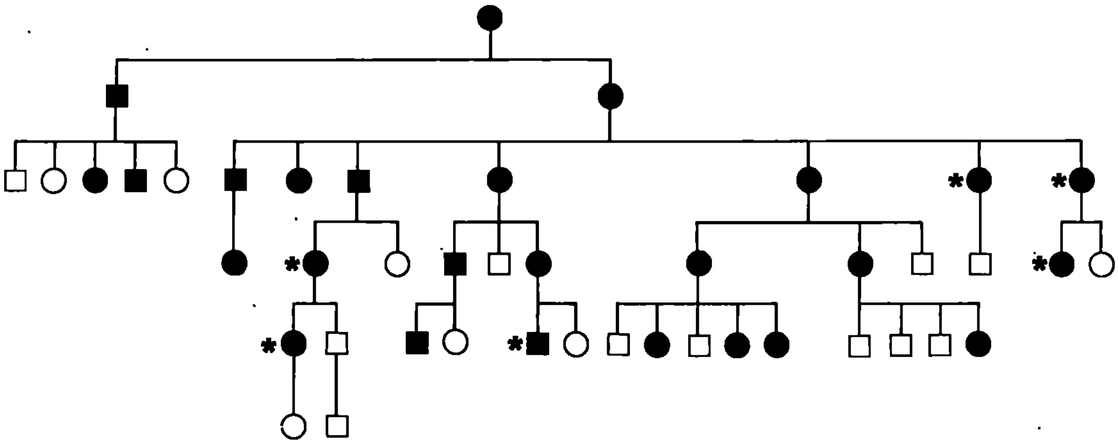

Fig. 3 *Dominantly inherited congenital corneal oedema. The solid symbols represent those affected. Those marked with * are under the care of Moorfields Corneal Clinic.*

Fig. 4 *An 11-year-old male with dominantly inherited corneal oedema. This patient had shown signs of progression and at the age of two had had a superficial calcified plaque excised.* A: *The cornea shows diffuse, variable oedema involving the stroma and epithelium.* B: *Slit photograph of the same eye. The acuity is 6/60.* C: *The same eye two months postoperatively. The acuity is 6/36.*

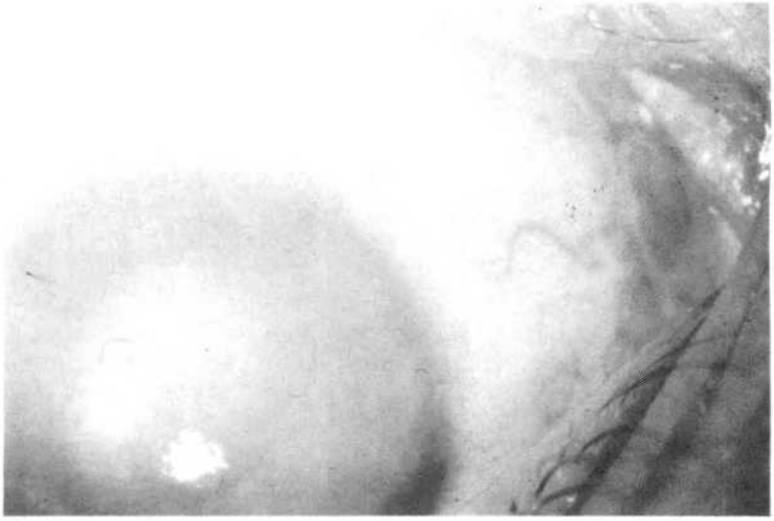

Fig. 4A

Results

SURGERY

Twenty patients underwent penetrating keratoplasty, nine unilaterally and 11 bilaterally, that is, 31 eyes had penetrating grafts. A total of 37 grafts were performed on these eyes. This included one eye which had a combined trabeculectomy and penetrating keratoplasty, having had a previous trabeculectomy. Follow-up was from six weeks to 11 years (mean 39 months).

Three patients did not undergo keratoplasty (Table 2). The age at which the first graft was performed in any individual is shown in Fig. 7. The size of the grafts varied from 6 mm to 8 mm (Fig. 8).

In those eyes receiving a graft the preoperative visual acuity was less than 6/60 except in three eyes, whose acuity was 6/24, 6/36, and 6/60 respectively.

The results of penetrating keratoplasty are summarised in Figs. 9-11. Penetrating keratoplasty resulted in a significant improvement of visual acuity in every eye while the graft remained clear. By six months after keratoplasty the majority of eyes (66%) attained a best corrected acuity of 6/18 or better, which is equivalent to an improvement of at least three lines on the Snellen chart. The acuity achieved

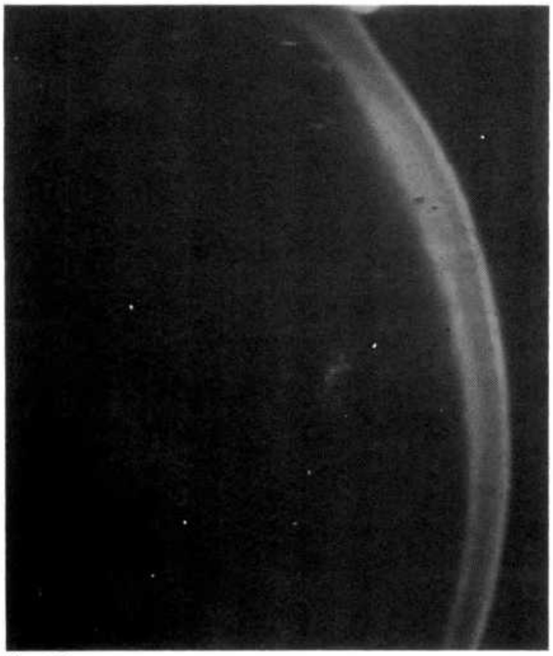

Fig. 4B

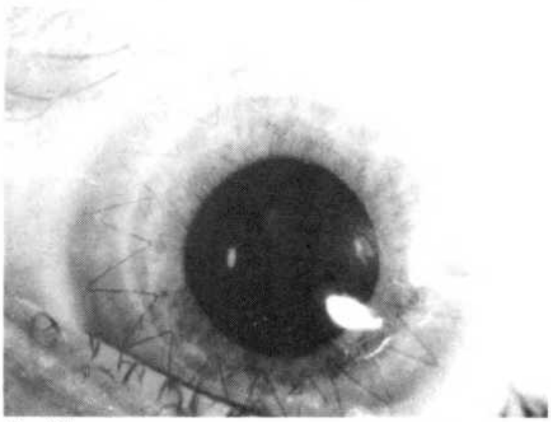

Fig. 4C

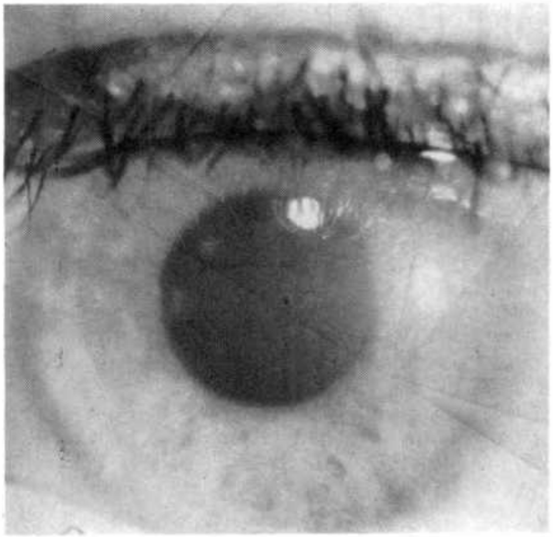

Fig. 5A

Fig. 5 *A 14-year-old male with a recessive inheritance pattern.* A: *The cornea shows diffuse stromal oedema which appears relatively mild. The acuity is <6/60.* B: *The same eye two months postoperatively. The acuity is 6/18.*

after successful keratoplasty did not correlate with the age at which the ocular abnormality was first observed or the age at which surgery was undertaken, though it is interesting to note that the three patients whose gain was least were also the oldest three patients at the time of surgery.

COMPLICATIONS

One patient showed a transient rise in intraocular pressure which reverted to normal following cessation of topical steroid therapy. Corneal graft rejection episodes were encountered in four eyes. In only one eye was this successfully reversed and the graft clarity preserved (Table 3). Of the other three eyes two were successfully regrafted and currently retain clear grafts. The remaining eye was regrafted on three further occasions, but all grafts were rejected. The rejection episodes were seen only in patients operated upon before 15 years of age.

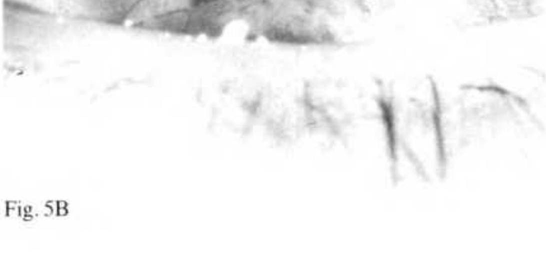

Fig. 5B

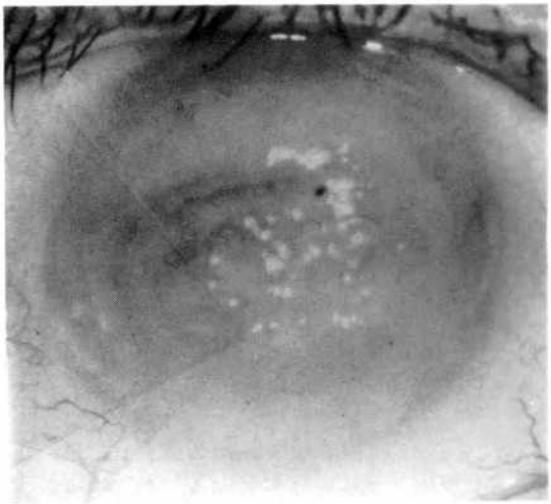

Fig. 6 *A 30-year-old female with a dominant inheritance pattern. The cornea is grossly thickened and the epithelium irregular. There is spheroidal degenerative change in the anterior stroma but little sign of vascularisation. This patient saw 6/12 postoperatively.*

One graft developed suppurative keratitis and became opaque. One eye suffered a traumatic rupture of the graft-host wound eight months following keratoplasty, with loss of lens, iris, and vitreous

Table 1 *Summary of those patients who had had previous glaucoma surgery*

Age	*Sex*	*Procedure*
21	F	Trabeculectomy
<1	F	Bilateral goniotomy
<1	M	Bilateral goniotomy and bilateral iris inclusion
<1	F	Bilateral trabeculectomy twice
<1	F	Bilateral drainage five times

Table 2 *Patients not undergoing surgery*

Sex	*VA R*	*VA L*	*Age*	*Other features*
M	6/60	6/36	13	Had goniotomy
M	6/36	CF	20	—
M	6/24	6/24	13	Manifest divergent squint

VA=visual acuity. CF=counting fingers.

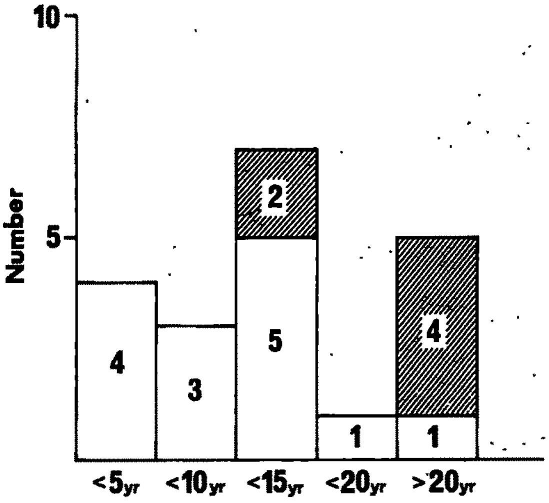

Fig. 7 *Age of patient when first graft performed.*

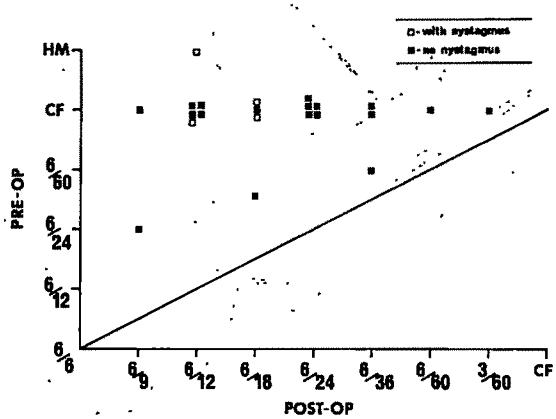

Fig. 9 *Preoperative acuity versus best corrected postoperative acuity in each eye receiving a graft. All eyes showed improvement in acuity. (Only those eyes with sufficiently long follow-up to permit accurate estimation of acuity are shown.)*

gel, and subsequent decompensation of the graft endothelium. This eye showed no evidence of a rejection episode.

There were thus only three failures out of 31 eyes (10%) to maintain a clear graft and useful vision.

HISTOLOGY

Light-microscopic (LM) sections from 26 corneas were reviewed. These included three patients not part of the clinical series of which two were previously reported on by Pearce *et al.*[14] Most of the specimens were of full thickness corneal discs. In some of the earlier cases only lamellar specimens were received, and Descemet's membrane and endothelium were not available for comment. Twenty cases, including nine from three generations of the autosomal dominant family, were examined. Electron microscopy (EM) of the cornea was performed on four members of this family (the two more senior members were previously reported on[14] in 1969). The EM results in the dominant group were compared with those of six corneas from five patients with the recessive form of the condition.

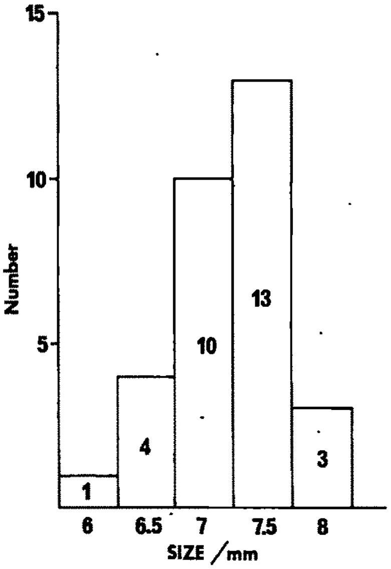

Fig. 8 *Size of first graft performed (by eyes).*

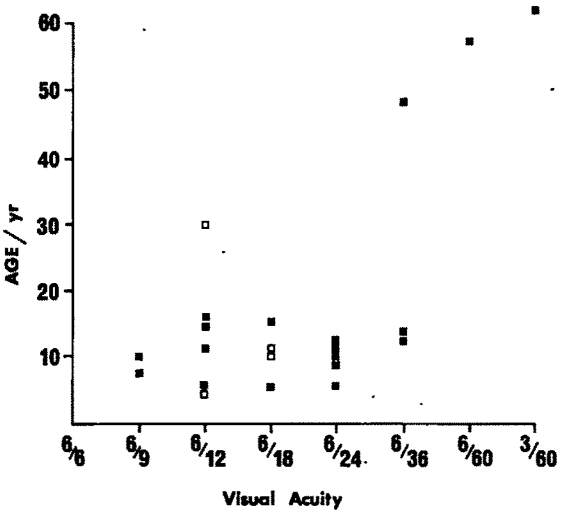

Fig. 10 *Age at surgery (by eyes) versus best corrected acuity. (Only those eyes with sufficiently long follow-up to permit accurate estimation of acuity are shown.)*

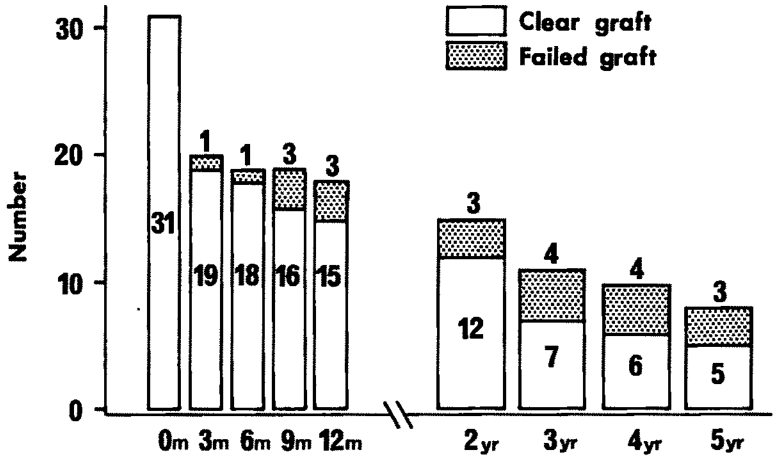

Fig. 11 *Graft survival against follow up. The numbers shown refer to the first graft in any eye. The survival of regrafts is not shown. Note the discontinuity of the time axis.*

Light microscopy

Changes were observed in all corneal tissues, and the results are summarised in Table 4. Marked atrophy of the epithelium was observed in five corneas from the dominantly inherited group and three from the recessives. Most epithelia showed basal oedema (Figs. 12, 13). Subepithelial fibrosis was more marked in the dominant group, seen in 60% of the biopsies but only in three of 16 from the recessive patients. Calcification of the subepithelial zone was present only in two of the dominant patients and none of the recessives (more was seen in the deep stroma at EM level).

Partial loss of Bowman's membrane was extremely common, seen to some extent in all of the dominant patients and all but two of the recessives. Stromal changes, at light level, were objectively confined to reporting the presence or absence of spheroidal (droplet) degeneration, present in six of the dominant group's biopsies but only in one recessive. Neovascularisation of the stroma was seen by LM in only two dominant patients; both of these patients had long standing disease presenting late for surgery.

The thickness of Descemet's membrane (DM) was measured in the majority of cases (at ×400) with an eyepiece graticule. Whenever possible the results were confirmed by EM. In the dominant group four DMs were in the range of 6–10 μm (Fig. 14), while three were much thicker—up to 21 μm in depth. None of the dominant group showed the more uniform thickening observed in some of the recessive patients, where measurements of 22–24 μm were seen. Only one DM in a 3-year-old child was of normal thickness. None of the recessives showed thinning or loss of definition of DM. Lamination, particularly under periodic-acid-Schiff staining, was not especially common. Retrocorneal fibrosis with a prominent posterior collagenous layer was seen in four cases, only one of which was recessive.

Endothelium was discernible in most of our cases, but loss of cells and degeneration were common. The changes ranged from atrophy with vacuolation to focal absence of cells. In some areas normal cells were seen. Multilayering of endothelial cells was demonstrable in only one case at light microscopic level. Melanin was seen in 14 of the 26 corneas, in attenuated endothelial covering cells.

Table 3 *Graft failures*

Cause	*Age at surgery (yrs)*					*Time after surgery*	*Comment*
	<5	*<10*	*<15*	*<20*	*>20*		
Rejection		1				4 m	Recovered
		1				3 yr	Failed, regraft clear
			4			8 m	Same eye, each graft failed, final failure not regrafted
				1		8 m	Regraft clear
Trauma			1			3 yr	Failed, not regrafted
Suppurative keratitis		1				3 m	Not regrafted

Seven rejected grafts in four eyes, out of a total of 26 eyes grafted. Only three eyes had opaque grafts.

Electron microscopy

Electron microscopy was used to characterise the apparently primary changes at the level of DM and the endothelium. Amorphous deposits of electron dense material were seen at the sites of spheroidal degeneration in two of the four dominant cases but in none of the five recessives examined. In two dominant cases the stroma had previously been reported as showing separation of lamellae, fragmen-

Table 4 *Light microscopic changes*

Case	*Age*	*Previous surgery*	*Epithelium*		*Subepithelial fibrosis/calcification*		*Bowman's zone deficiency*	*Stroma*		*Descemet's membrane*		*Endothelium*		
			Atrophy	*Basal oedema*				*Vessels*	*Spheroidal degeneration*	*Max width µm*	*Lamination*	*Deficiency*	*Multilayer*	*Melanin*
Dominant														
1a	62	–	+	+	+	–	++	+	+	6–7	–	++	–	+
1b	65	–	+	–	+	+/–	++	+/–	+++	19–21	+	++	–	+
2	57	–	+	–	+	–	++	–	+	19–21	+	++	–	–
3	58	–	++	+	+	–	++	–	+	n/a	+	++	–	–
4	20	–	–	+/–	+	–	++	–	–	14	–	+/–	–	–
5a*	4	–	–	–	+	+	++	–	+					
5b	14	–	+/–	–	–	–	++	–	–	7		+/–	–	–
6	31	+	+/–	+	–	–	+/–	+	+	6–7		+	–	+
7*	37	–	++	–	–	–	+	–	–	6–10		++	–	+
8	6	–	+	–	–	–	+	–	–	n/a				
Recessive														
10	7	–	–	–	–	–	+/–	–	–	9–10		–	–	–
11	24	–	+	+	+	–	++	–	+	24	+	+/–	–	–
12	14	–	–	+	–	–	++	–	–	14	–	–	–	–
13	20	–	–	+	–	–	+	–	–	17·5	–	+	–	+
14a	15	+	+/–	+	–	–	+/–	–	–	22·5	–	+	–	+
14b	17	+	–	–	–	–	–	–	–	17·5	–	+	–	+
15	7	–	–	–	–	–	–	–	–	14	–	+/–	–	–
16	11	–	–	–	+	–	+	–	–	14–17·5	–	+/–	–	–
17a	16	+	+/–	+/–	+/–	–	+	–	–	14	–	+	–	+
17b	19	+	+	+/–	–	–	–	–	–	10	–	+	–	+
18a	5	–	–	+	–	–	+	–	–	19·5	–	–	–	–
18b	7	–	–	+	–	–	++	–	–	10	–	–	–	–
19a	4	+	–	+	–	–	+/–	–	–	12	–	+/–	–	–
19b	5	+	–	+	–	–	+/–	–	–	11–13	–	+/–	–	+
20a	3	–	+/–	+	–	–	–	–	–	3·5				
20b	8	–	–	+	–	–	–	–	–	9–14	–	–	+/–	–

*Lamellar specimen only.

tation and disorganisation of collagen fibres, and degeneration in keratocytes.[14]

In the four dominant cases DM was predominantly thickened by an irregular increase in thickness of the posterior non-banded portion, while the anterior banded zone was of normal thickness and arrangement (Fig. 15). In these cases an irregular felt-like or bird's nest-like (on SEM) array of matted collagen fibrils was laid down without an orderly pattern, with little basement membrane-like material but with small foci of long-spacing collagen (Fig. 16). This irregular thickening, forming a posterior collagenous layer, was in contrast to the recessive group.

Five recessive cases (six corneas) were examined with TEM; scanning electron microscopy (SEM) was performed in two. Descemet's membrane was evenly thickened. The anterior banded zone was regularly and normally thick. The non-banded zone showed a homogeneous thickening by a more organised deposition of basement membrane-like material, and focal long-spaced collagen, mixed in an orderly matrix with fine fibrillary collagen. No evidence of the bird's-nest disorganised pattern was present as seen in the dominant cases.

Membrane bound melanin granules were seen on both TEM and SEM of dominant cases inside rounded or humped endothelial cells (Figs. 17, 18). Parts of the thickened disorganised Descemet's membrane were bare, without a covering of endothelial cells. In one dominant case there was obvious overgrowth of cells, covering more effete rounded cells with vacuolated cytoplasm. The posterior covering cells were more electron dense, with more organelles present.

Frank multilayering of cells was apparent only in the younger recessive case examined. In the recessive group as a whole there was slightly less tendency for healthier cells to become flattened in an attempt to cover up the effete electron lucent cells. Some areas appeared normal on SEM, but the cratered, vacuolated cells were present in recessive cases. Few of the cells examined in detail showed the marked melanisation seen at light microscopy (Figs. 19A, B).

Discussion

Although histological studies indicate variations in the pattern of developmental abnormalities of the

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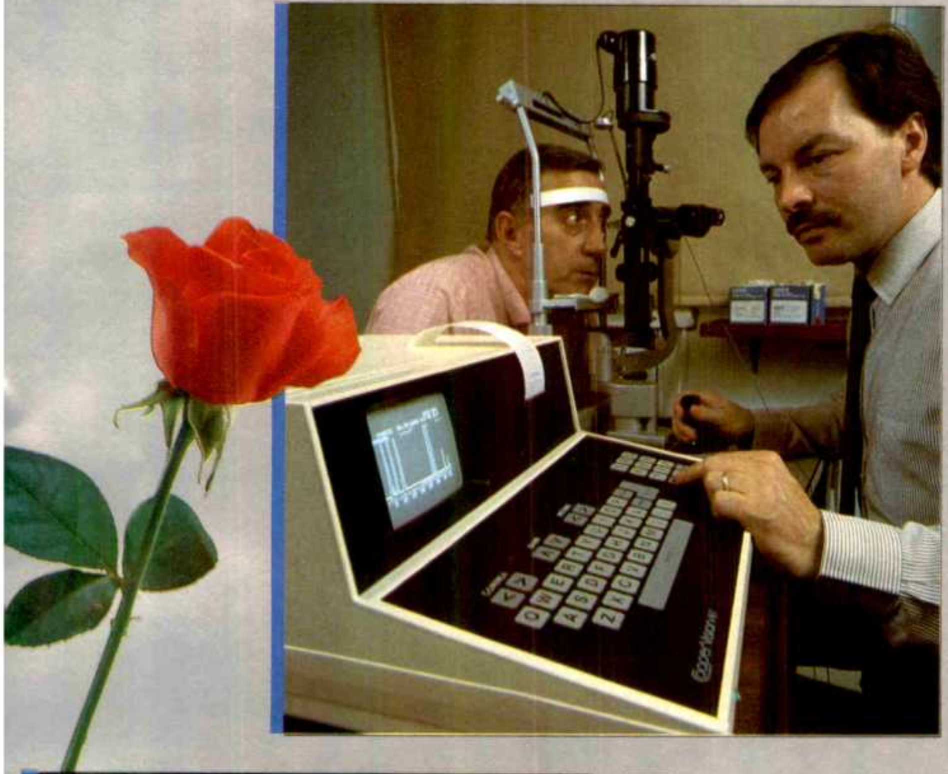

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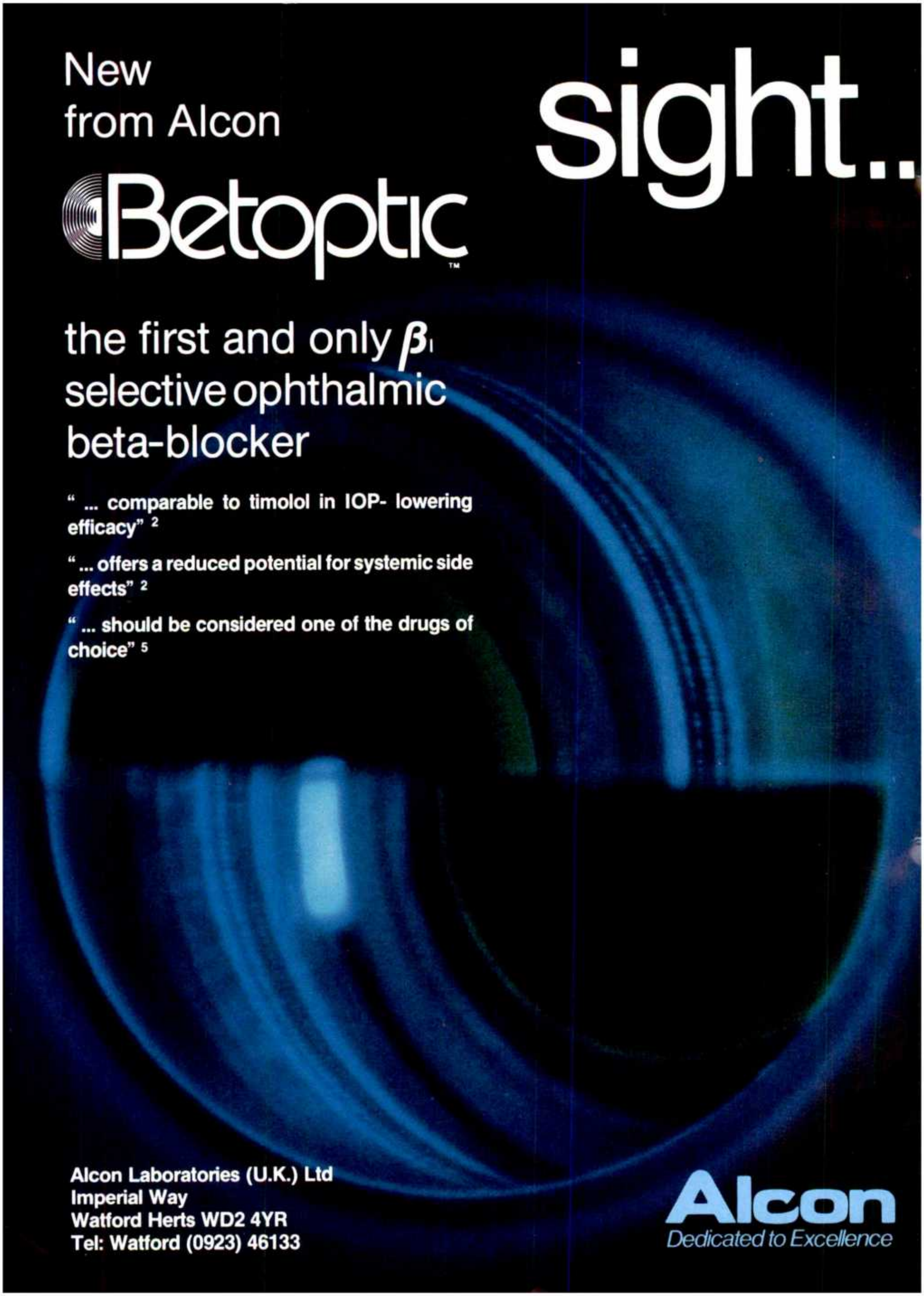

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REFERENCES: 1. Berrospi A. R. and Leibowitz H.M. Betaxolol. A new beta-adrenergic blocking agent for treatment of glaucoma. Arch. Ophthalmol. **100** 943-946 June 1982. **2.** Berry D.P., et al., Betaxolol and Timolol. A comparison of efficacy and side effects. Arch. Ophthalmol. **102** 42-45 January 1984. **3.** Levy N.S., et al., A controlled comparison of Betaxolol and Timolol with long-term evaluation of safety and efficacy. Glaucoma **7** 54-62 March-April 1985. **4.** Schoene R.B., et al., Effects of topical Betaxolol. Timolol and placebo on pulmonary function in asthmatic bronchitis. Am. J. Ophthalmol. **97** 86-92 January 1984. **5.** Stewart R.H., et al., Betaxolol vs Timolol. A Six-Month double-blind comparison. Arch. Ophthalmol. **104** 46-48 January 1986. **6.** Van Buskirk, E.M., et al. Betaxolol in patients with glaucoma and asthma. Am. J. Ophthalmol. **101** 531-534 May 1986. **7.** Data on file at Alcon Research and Development.

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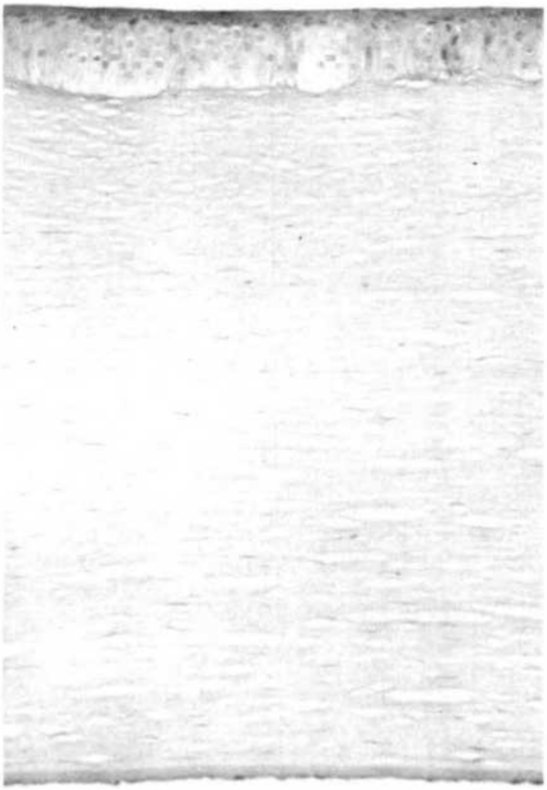


Fig. 12 *CHCO (recessive). The basal layers of the epithelium are oedematous, there is loss of Bowman's zone, and Descemet's membrane is slightly thickened (14 μm) with a lining of degenerate endothelium periodic acid-Schiff.*

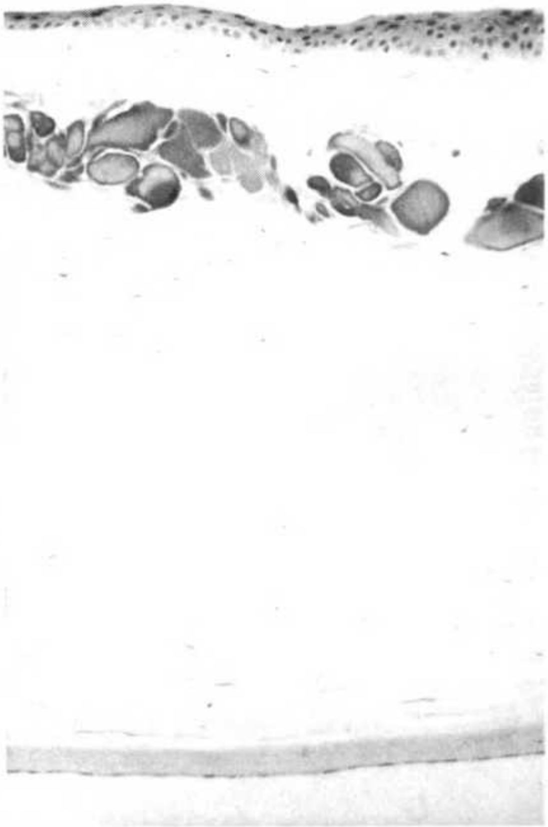


Fig. 13 *CHCO (recessive). Moderate atrophy and oedema of the epithelium is seen with partial loss of Bowman's zone and deposition in the superficial stroma of homogeneous protein material characteristic of spheroidal droplet degeneration. Descemet's membrane is considerably thickened (24 μm) and has an atrophic endothelial lining. Haematoxylin and eosin.*

corneal endothelium, congenital hereditary corneal oedema of Maumenee (CHCO) appears to be a single, specific clinical entity characterised by the finding at or soon after birth of diffuse corneal oedema affecting both eyes symmetrically without other significant developmental abnormalities of the anterior segment of the eye. The main differential diagnosis is from congenital glaucoma and the mucopolysaccharidoses. CHCO should be readily distinguishable from congenital glaucoma by the finding of a normal corneal diameter, the absence of splits in Descemet's membrane or of any abnormality of the iris, and a normal intraocular pressure. It is noteworthy that in our series of 23 patients five had undergone surgery for glaucoma previously, four having had two or more operations in early infancy for 'congenital glaucoma'. Previous authors have reported similar instances.[13 15]

In the case of mucopolysaccharidosis the corneal opacities are in the nature of an infiltration rather than oedema, and usually there are other clinical or biochemical features that may confirm the diagnosis.

Posterior polmorphous dystrophy, if advanced, may appear similar to CHCO both clinically and histologically, and some authorities have considered that it may represent part of the spectrum of the same developmental anomaly.[20]

With regard to the natural history of CHCO, in seven of our cases there was evidence of progression. Maumenee described a similar progression in two of his original cases and Keates and Cvintal[15] described a family with a typical recessive pattern who also showed signs of progression. The usual course is, however, for the oedema to remain unchanged for many years. Some temporary regression of the

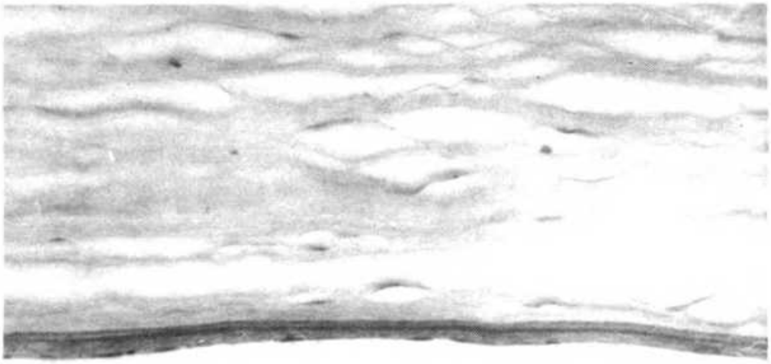


Fig. 14 *CHCO (dominant). Descemet's membrane is not significantly thickened (8 µm) but shows lamination with well defined anterior banded and posterior non-banded zones and a posterior collagenous layer (6 µm) covered by attenuated endothelium. Periodic acid-Schiff.*

oedema during childhood is occasionally seen, as in at least one of our cases, but never to complete normality.

It is remarkable that, in spite of significant corneal clouding from birth, visual development is often little impaired, as shown by substantial improvement of visual acuity following keratoplasty even if this is delayed into adolescence or adulthood. The infrequency of nystagmus may also support this contention. Nystagmus is in any case of little predictive value as to the visual potential following keratoplasty.

Allograft reactions were not a frequent occurrence, but only one graft out of four affected recovered from a rejection episode. When those grafts in patients under 15 are considered (26 eyes), our figure of four eyes with rejections and a total of three failures overall from any cause compares favourably with previously published figures for penetrating keratoplasty in children.[21-23]

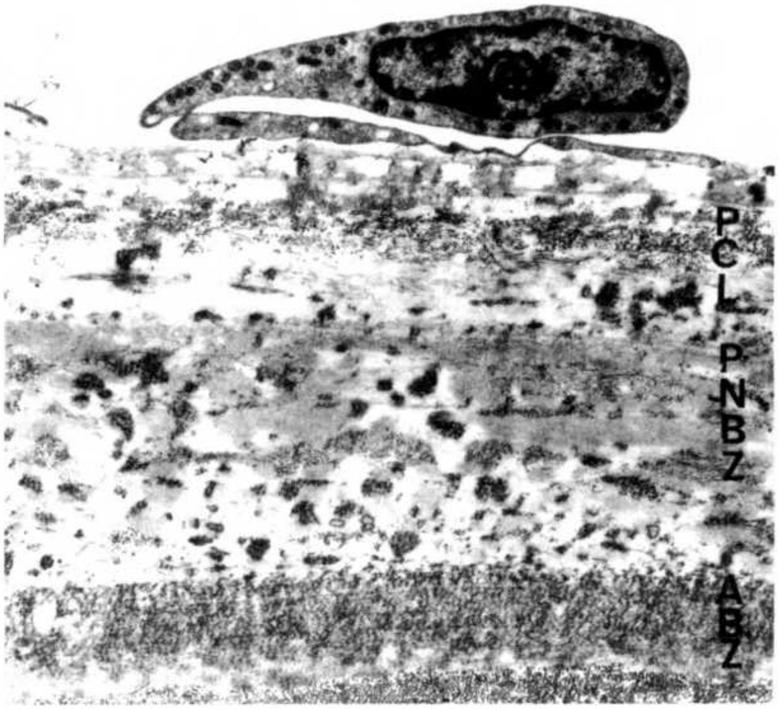


Fig. 15 *CHCO (dominant). Posterior collagenous layer below endothelial cell and above normal anterior banded zone and thick posterior non-banded zone.* × *12 000* PCL=*posterior collagenous layer.* PNBZ= *posterior non-banded zone.* ABZ=*anterior banded zone.*

Table 5 *Electron microscopic changes*

Case no.	*Age*	*SEM*	*Surgery (previous)*	*Descemet's membrane*				*Endothelium*			
				Ant. banded zone	*Post non-banded zone*		*PCL (fibrillary)*	*Absent*	*Vacuolated*	*Multi-layered*	*Melanin*
					BM-like material	*longspaced collagen*					
Dominant											
1B	65	+					++	+			
5B	14	−		Normal	+	+	+	+	+	+	
7	37	−		Normal	−/+	++	++	+		−	
9	63	−		Normal	−/+	+	++			−/+	++
Recessive											
12	14	+		Normal	+	+	−	+/−	++		
14A	15	+	+	Normal	++	++	+/−				
18B	7	+		Thick	++	++	−	++	+		
19	5	−	+	Normal	++	+	+		+		+
20A	3	−		Thin-Normal	++	+	−		+	+	
20B	8	−		Normal	+	+	−		+	++	

Our observations lead us to caution against penetrating keratoplasty in early childhood for CHCO. It seems prudent in most cases to delay surgery until the visual disability can be properly assessed in the knowledge that delay does not appear to prejudice visual results in a successful graft. It is our view that the hazards of corneal graft surgery in infants far outweigh the advantages to be gained from early surgery in this condition. We consider it is reasonable to conclude from our series that penetrating keratoplasty has a relatively good prognosis in CHCO and is justified in patients whose visual disability warrants it.

Two distinct patterns of inheritance have been described in this condition by Judisch and Maumenee.[18] They did not examine any patients from a dominant pedigree themselves but quoted the family reported by Pearce *et al.*[14] This is the same family (several years earlier) as the one we present. Typically, the recessive type is said to be found earlier and not to be progressive, in contrast to the dominant pattern. We found a few cases which were clearly progressive in both groups. Presentation may be later in the dominant group for reasons other than poor sight—for example, because the families are familiar with the condition and believed until recently that surgery would not be of benefit to them. It is interesting to note that in successive generations of our dominant family presentation has been progressively earlier. Associated symptoms of photophobia are uncommon, but, if the oedema is longstanding, secondary degenerative changes may be

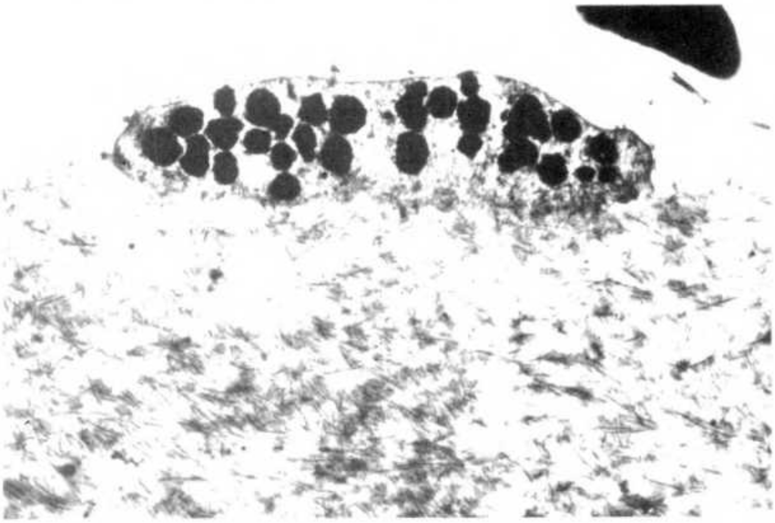


Fig. 16 *CHCO (dominant). Endothelial cell containing individually membrane bound melanin granules (melanosomes) lying above bird's-nest fibrillary non-specific posterior collagenous layer.* × *13 200.*

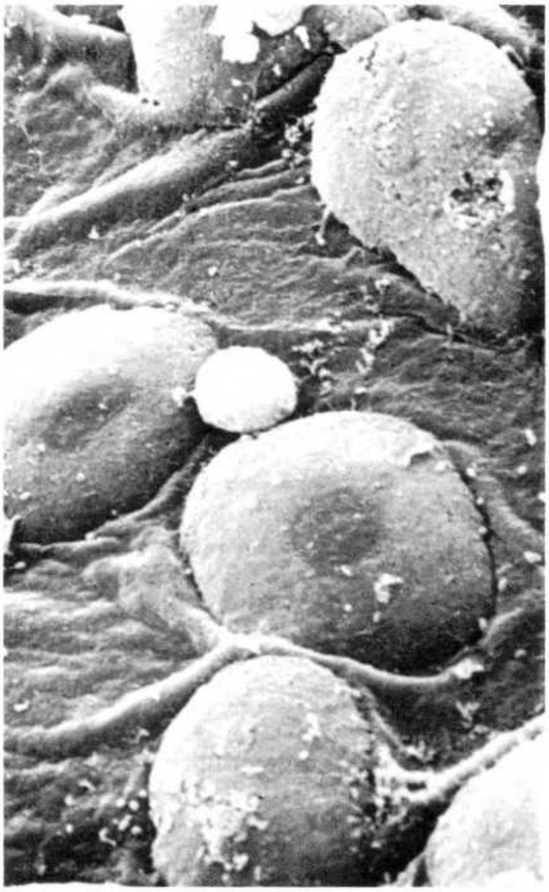


Fig. 17 *CHCO (dominant). Humped endothelial cells and bare Descemet's membrane. SEM, × 1133.*

seen. Nystagmus may be found but infrequently in both groups. We do not believe it is possible to differentiate between the dominantly and the recessively inherited patterns from the clinical features alone.

HISTOLOGY

Following Maumenee's description[8] of the clinical features and some of the histological features of this complex endothelial dystrophy, a number of authors, whose reports were summarised by Waring *et al.*,[24] illustrated different facets of the disease. Most authors agree that the epithelial and basement membrane changes, which are probably secondary in nature, consist of variability of thickness, from three to seven layers of cells, with focal loss of polarity and intracellular oedema, especially at the base of the epithelium. Frank ulceration is unusual. While Bowman's layer has been reported as being intact, we found most of our cases showed some disruption.

The clinically observed stromal oedema is much harder to assess histologically. Although slit-lamp examination and measurement of the thickness of stroma may be difficult or even impossible without ultrasonic pachymetry, histological measurements are probably even more inaccurate, since artefact is difficult to control. In this review we decided therefore not to measure stromal thickness or to comment on the diameter of stromal collagen fibrils, or to attempt to assess the amount of fluid separating the fibrils or lamellae. We did note in two of our longstanding but genetically indisputable cases of autosomal dominant disease neovascularisation of the corneal stroma. Previously this has not been reported, but this may be because the dominant condition is much less common and fewer cases have been examined. These two cases also showed spheroidal degeneration, which is almost certainly a reflection of the longstanding nature of the disease. It is interesting that our oldest recessive patient also showed this, although, arguably, there may have been a climatic (actinic) contribution as well, which could have accelerated the process.

We were fortunate in having Descemet's membrane and endothelium to examine in most cases. Some earlier work was impaired by artefactual loss of these structures and consequent inability to recognise the underlying pathogenesis of stromal oedema. It is well known that shearing forces during surgery and histological preparation can cause artefactual loss of cells which may not reflect the appearance in vivo. We observed, on SEM, vacuolation and ulceration of endothelial cells. Such degeneration is, however, a focal process, endothelial cells in some areas being present in normal numbers and of a size relative to the age of the patient.[25]

The variability in the nature of the endothelial cells is further evidenced in one case examined by SEM, wherein the endothelium was (within one SEM biopsy) thinned, ulcerated, vacuolated, heaped up in double layers, and even normal, and this may explain the conflicting reports on the nature of changes in the endothelial cells in this condition. Similarly, the amount of thickening of Descemet's membrane, and the nature of that thickening, might be expected to vary above the endothelial cells according to the stage in the dystrophy at which the cells degenerate. This may explain the wide range of reported abnormalities in the literature, which vary from absence[14] (probably artefactual), thinned,[9 10 13 16 17 26] to thickened[12 14 17] with multilamination of the endothelium.[11]

If Descemet's membrane and any underlying acquired posterior collagenous layer[27] (PCL) can be regarded as an 'archaeological record'[19] of the insults suffered by the membrane as a result of endothelial cell dysfunction, then the variation in the mem-

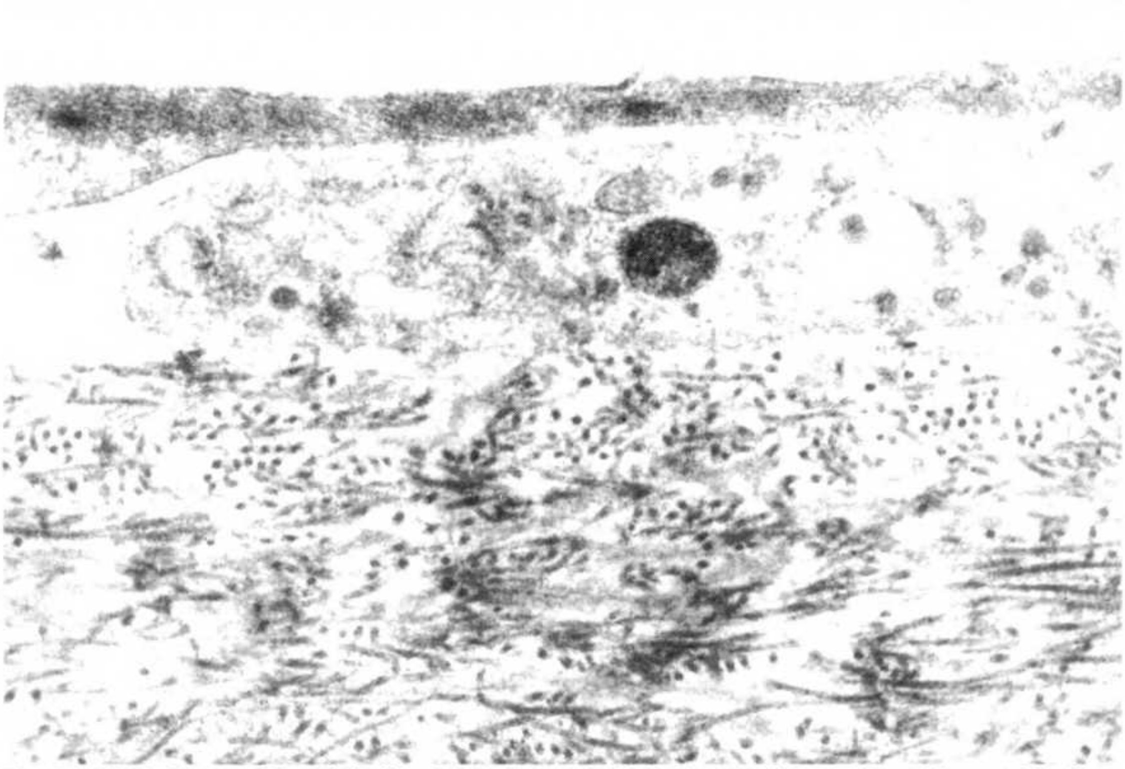


Fig. 18 *CHCO (dominant). Rounded, effete, electron dense endothelial cells covered by more electron dense, viable cells. Note bird's-nest fibrillary collagen pattern in posterior collagenous layer.* × *40 000.*

brane's structure should reflect the variation in physiological circumstances and function of the endothelial cell beneath. We did observe that non-specific bird's-nest pattern of fibrillary collagen deposited as a PCL[27] was more common in the autosomal dominant group. This type of PCL has been described following a wide variety of traumatic conditions as well as in CHCO. In at least some of our cases it could not be attributed to previous surgery. We did not observe the fibrocellular type of PCL,[27] though this may be a possible variant, especially in those cases where fibroblastic metaplasia of endothelial cells has been observed.[10 16] It is interesting that in the dominant group the anterior banded zone of Descemet's membrane was present and of normal thickness. This supports the contention that, in utero, the function of endothelial cells between the third and eighth month of gestation was normal, permitting normal secretion of collagen and banding of this zone. This phase of anterior zone (ABZ) growth in normal corneas appears to occur at a faster rate than the secretion of the posterior non-banded zone, as the whole of the three μm thickness of the ABZ is laid down in four months while the subsequent deposition of the posterior non-banded zone takes longer, with accumulation of the mixed basement membrane and collagen material occurring at a slower rate, with a more gradual slope on the growth curve.[28 29] In both our autosomal dominant and recessive groups the thickness of the whole Descemet's membrane is greatly increased, and the distribution of the results of the thickness compared with the predicted thickness (Fig. 20) seems to point to growth at the accelerated prenatal phase rate continuing after birth, without the usual slowing down, especially in the recessive group. This makes the observation from our cases of recessive disease—that Descemet's membrane is usually thickened not by a non-specific fibrillary PCL but by accumulation of normal, posterior, non-banded zone material (mixed collagen and basement membrane)—even more fascinating. It implies that the normal restrictive pattern of endothelial synthesis and secretion is not enforced.

There does appear to be a subtle difference between dominant and recessive cases, both quantitatively in the thickness of collagen laid down in the expansion of Descemet's membrane and in the apparent rate of such deposition. Qualitative differences are also seen in the increased tendency of the deranged endothelium to lay down a normally constituted, homogeneous, posterior, non-banded

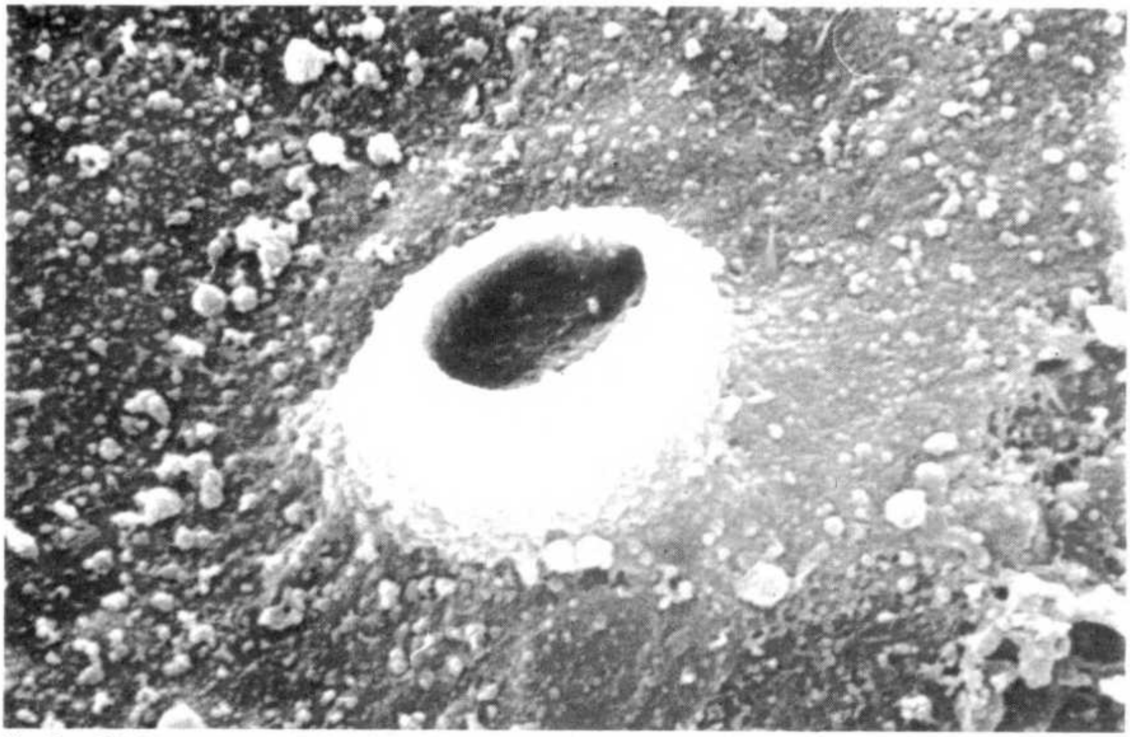
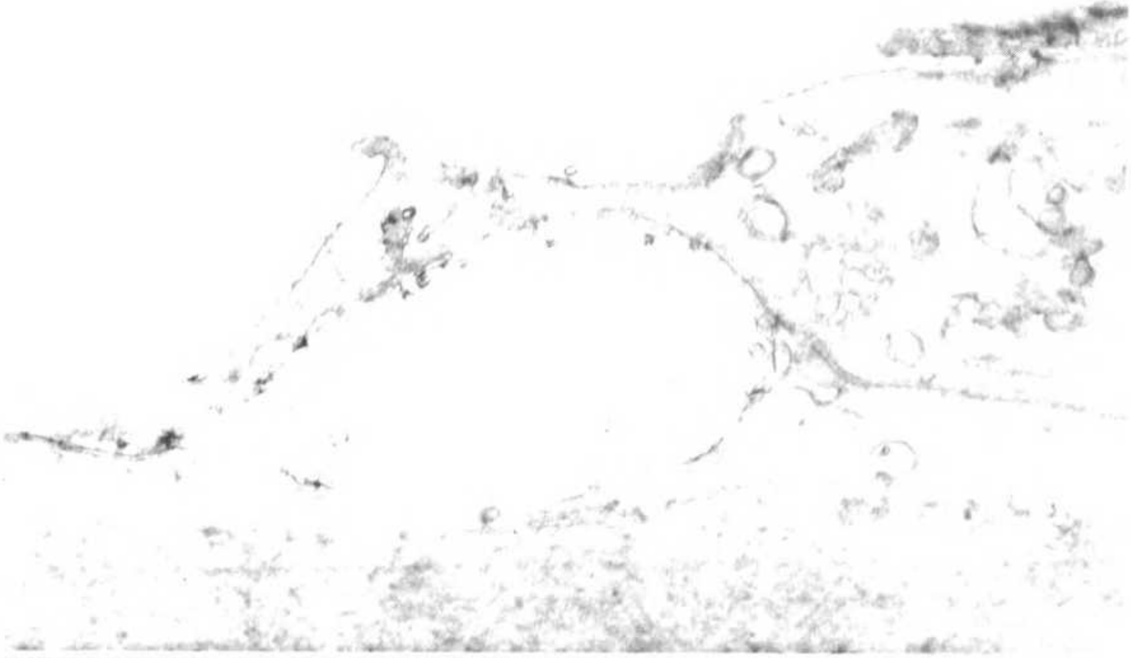


Fig. 19 *CHCO (recessive).* A: *Endothelial cell. Note microvilli projecting into the lumen of the crater. SEM, × 20 000.*



B: *Endothelial cell with vacuole with microvilli projecting into it. × 26 000.*

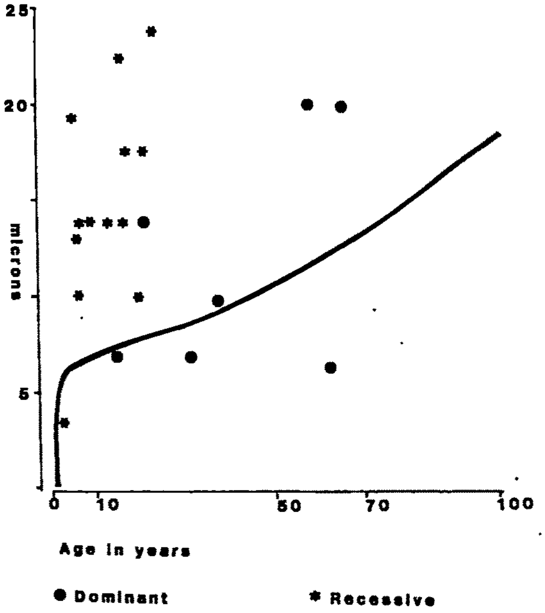


Fig. 20 *Measurement of the thickness of Descemet's membrane compared to curve of predicted values for age.*

Descemet's membrane in the recessive cases, with an accelerated rate of deposition, rather than a reactive fibrillary posterior collagenous membrane.

The changes in Descemet's membrane ideally should mirror those seen in the endothelium. If the underlying endothelial cells are absent or attenuated, then it is inevitable that the formation of Descemet's membrane will be arrested at the stage when the cell is lost. Non-specific reactive fibrillary change might also be expected if there has been fibroblastic metaplasia.[10 16 23] We could not demonstrate endothelial cell intracytoplasmic filaments in our cases. We did see multilayering of cells, but not the marked low cuboidal embryonic type of cells described as being 'intermediate'[23] in a case with some features (at histological level) of posterior polymorphous dystrophy (PPD). PPD, it has been claimed, is a related condition to CHCO, and one case of ours, a recessive, showed epithelium-like cells with marked multilayering accompanied by a thin Descemet's membrane at age 3, but a thicker than usual Descemet's at the time of keratoplasty on the second eye at the age of 8 years. These epithelium-like cells are usually associated with PPD, but this case was clinically indistinguishable from other cases of CHCO according to our criteria.

The corneal endothelium develops from the neural crest[30] and, as such, the cells are thought to be pluripotential. This has been used as a basis for recent reclassification[31] of the diseases affecting endothelium and also as an explanation of the metamorphosis of endothelial cells into fibroblastic and epithelium-type cells. The incidence of melanin in 'endothelial cells' in our series was quite high, and others have reported their presence in CHCO. The presence of melanin within endothelial cells has been thought to be due either to phagocytosis of melanin liberated from anterior border cells or to migration of such cells to cover bare Descemet's membrane and maintain its structural integrity.[32 33] The electron microscopy of the melanin granules shows them to be melanosomes, of the smaller size associated with other neural crest derived melanocytes, rather than engulfed particles within phagolysosomes. Although these cells could have migrated from the anterior border, it is tempting to describe these melanocyte-like cells as another example of the metaplastic range of the endothelial cell.

Degeneration in the form of vacuolation was first described by Pouliquen *et al.*[34] and we demonstrated these cistern-like vacuoles clearly, both in SEM and TEM. The overriding of cells, which appear to be an effort to cover ineffectual (presumably leaky) endothelial cells, have not been described before in CHCO.

Our findings support the hypothesis that in cases with thinned or attenuated Descemet's membrane, complete endothelial dysfunction occurs in utero, so that only fetal ABZ is secreted. Thick Descemet's membrane on the other hand is the probable result of persistent dystrophic endothelium secreting a posterior collagenous layer.[19] In addition, however, we would like to postulate that the process, in the recessive group especially, also constitutes a persistent failure of growth regulation, leading to accumulation of a functionally abnormal and structurally exaggerated form of posterior non-banded Descemet's membrane.

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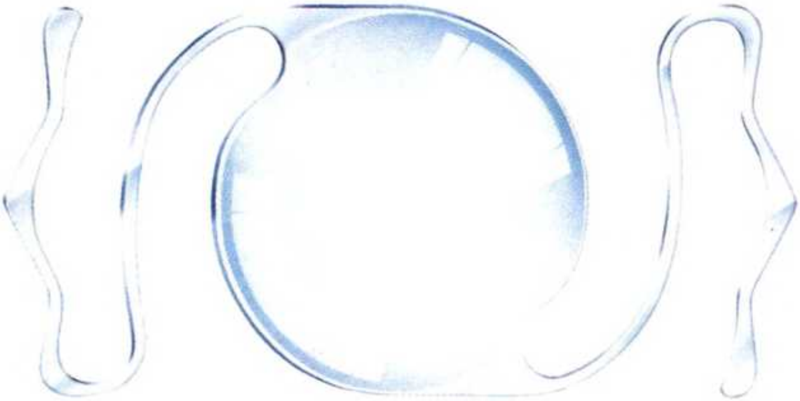

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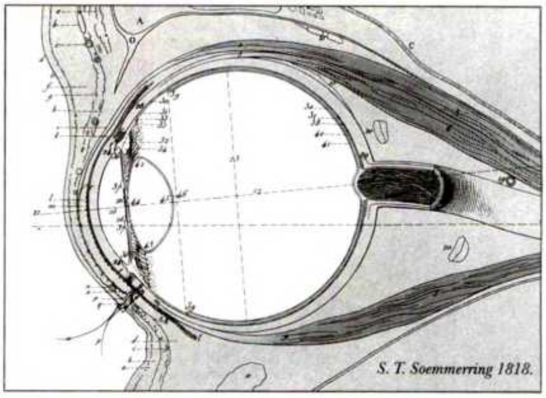

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Fluorescein angiography in the differential diagnosis of sclerokeratitis

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SUMMARY Anterior segment fluorescein angiography has been used in the investigation of patients with sclerokeratitis. This showed that corneal thinning or destruction was associated with non-perfusion of the episcleral vasculature. The changes arose either as a result of a systemic vasculitis in seropositive individuals or were induced by surgery to the eye. Infiltrative forms of sclerokeratitis were commoner in seronegative patients and were less often associated with vascular shutdown.

Destructive sclerokeratitis is a disastrous condition which can lead to loss of the eye through perforation. If it is treated vigorously and early, the prognosis is good, but an accurate diagnosis is vital if the correct treatment is to be given. Although some corneal change is found in 29% of patients with scleritis and 15% of patients with episcleritis, this becomes of importance only when the optical axis is obscured by opacities or when destructive changes occur. Early detection of the more serious forms of keratitis enables effective treatment to be instituted before the vision becomes affected. Anterior segment angiography has proved of considerable assistance in detecting the serious forms of this condition, and its efficacy as an aid to diagnosis is discussed in this paper.

The changes in the cornea in episcleritis are never severe and rarely permanent and result either from an extension of localised scleral oedema into the cornea, or to dellen formation caused by drying of an area of cornea adjacent to a region of intense episcleral oedema near the limbus.

Several distinctive patterns of corneal change are found in patients with scleritis. The changes are usually related to or in the same quadrant as the active scleral disease and may or may not be associated with vascularisation of the cornea.

Diffuse stromal keratitis is usually of rapid onset, occurring in the active stage of scleral inflammation. Superficial or mid stromal opacities appear within the corneal stroma and unless treated expand slowly, becoming surrounded by dense white 'precipitin ring'. If the reaction is intense, keratic precipitates may aggregate on the posterior corneal surface in the area of the stromal opacities.

Sclerosing keratitis may arise from a diffuse stromal keratitis which has failed to resolve completely or may arise de novo. The cornea changes to resemble sclera. The stromal opacifies containing lipid often looking like crystals of candy floss. The changes often start at the periphery but may advance towards the centre with alarming rapidity. If any vessels are present, they never occur at the advancing edge of the opacity.

Deep stromal keratitis is an unusual change in which a white opaque sheet of tissue invades the periperal cornea lying deep on Descemet's membrane. There may occasionally be an associated nummular corneal stromal opacity.

LIMBAL GUTTERING AND KERATOLYSIS

These are the most serious forms of corneal involvement in scleritis but present in various forms which need to be distinguished from each other.

(*a*) *Limbal corneal thinning (contact lens cornea).* The most benign form is one in which the peripheral cornea becomes thinned gradually over many years to resemble a contact lens on the cornea. All these patients have longstanding rheumatoid arthritis.

(*b*) *Terriens-like changes:* In this form the limbus becomes thinned within 2-3 mm of the limbal margin in the region of the active scleral disease. The region affected becomes opaque, vascularised, and occasionally extremely thin.

(*c*) *Acute stromal keratitis and keratolysis.* In very severe scleritis, areas of the central and peripheral

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Correspondence to P G Watson, FRCS, 17 Adams Road, Cambridge.

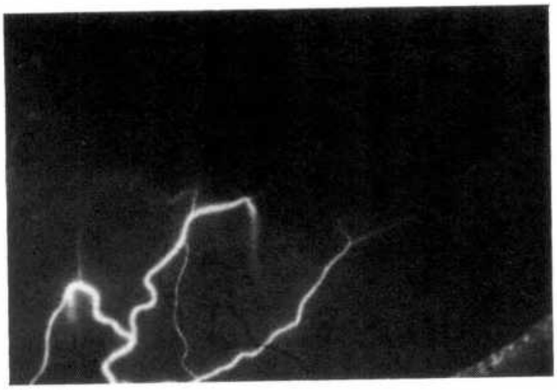

Fig. 1A

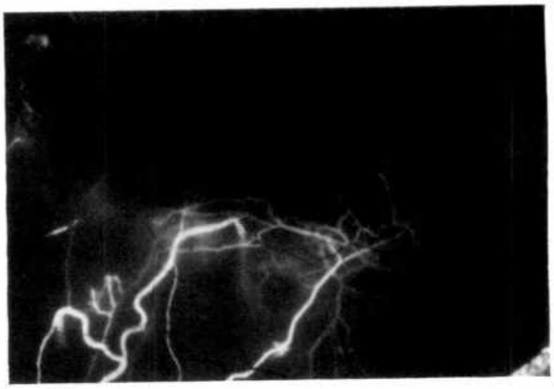

Fig. 1B

Figs. 1A, B, C Group 1A *Anterior segment fluorescein angiogram from a patient who had rheumatoid arthritis and a vascularised corneal gutter.* (A) *Early arterial phase. Large perforating vessels fill rapidly.* (B) *Early venous phase. The capillary network is patchily filled at the limbus only. The more proximal network is not perfused. The abnormal vessels in the cornea are filling from deep vessels arising deep to the sclera.* (C) *Late venous phase. There is still very poor filling of the capillaries at the limbus, and these vessels are grossly abnormal. There is deep and superficial leakage of dye. The proximal episcleral network is still unperfused.*

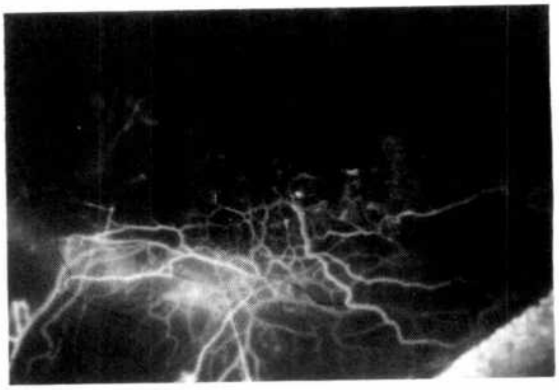

Fig. 1C

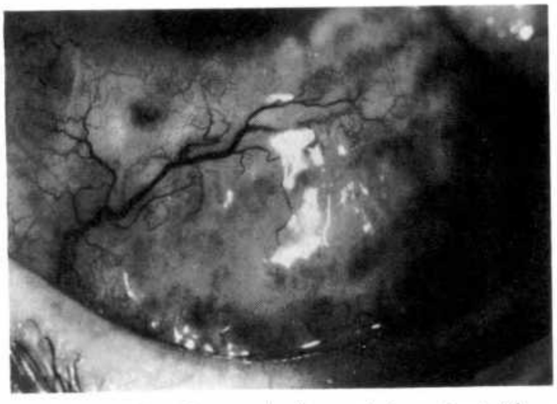

Fig. 2 Group 1A *Corneoscleral necrosis in a patient with Wegener's granulomatosis. The destructive process not only involves both large areas of sclera but transgresses the limbus. Perirarteritis nodosa and Wegener's granulomatosis are the only conditions in which this occurs.*

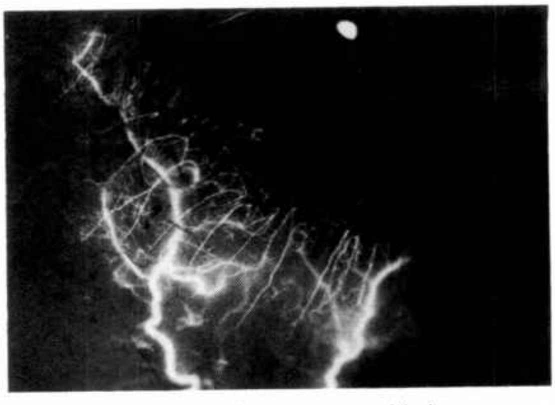

Fig. 3 Group 1A *A similar appearance of the late venous phase to Fig. 1 in a patient who had an active sclerokeratitis but who had no overt connective tissue disease and had strong positive antinuclear and anti-DNA antibodies. Note the gross abnormality of the occluded capillaries.*

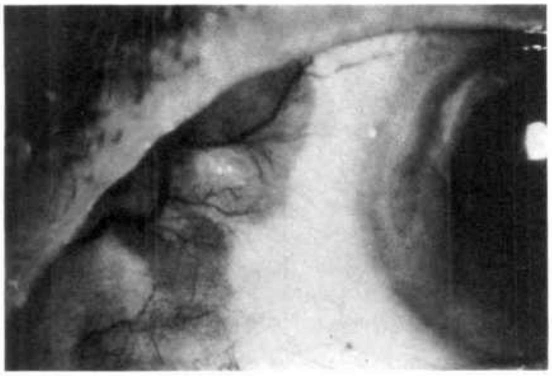

Fig. 4A

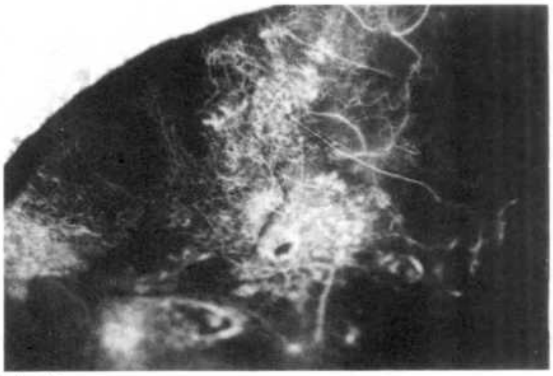

Fig. 4B

Figs. 4A, B Group 1B (A) *Corneal gutter associated with a scleritis which followed extracapsular cataract extraction and posterior chamber lens implantation. The region adjacent to the limbus is white. In the area of intense scleral inflammation there are areas of scleral necrosis.* (B) *Anterior segment fluorescein angiogram at the limbus at the lower end of the gutter. Late venous phase. The gutter is vascularised from both superficial and deep vessels. There are some areas of conjunctival capillary dropout and some of the episcleral vessels do not fill. The whole vascular pattern is abnormal.*

cornea opacify and swell. Initially the lesions are isolated, white or grey, but rapidly coalesce so that large areas of the cornea may become involved. Keratic precipitates are sometimes seen on the endothelium under the opacities whether a uveitis is present or not.

(*d*) *Peripheral corneal melting*. This condition starts as a grey, swollen, infiltrated area adjacent to an area of scleritis which rapidly breaks down, or, if there are several such areas, they coalesce to extend around the limbus. The gutter usually has a sharp well defined border on the limbal edge, but both the limbal and corneal margins may be undermined. Fine vessels extend to the edge of the ulcer, which in the early stages looks very like a Mooren's ulcer except for the intense scleral (as opposed to limbal) inflammation. Although this is the usual pattern in patients with scleromalacia perforans (necrotising scleritis without inflammation), the scleral inflammatory response is often very limited.

Observations

Forty-five patients who were attending the Scleritis Clinic at Moorfields Eye Hospital, City Road, London, and Addenbrooke's Hospital, Cambridge, were investigated. All had documented evidence of scleral and corneal disease and had had anterior segment fluorescein angiography performed.

Each patient was assessed for: (1) The type and

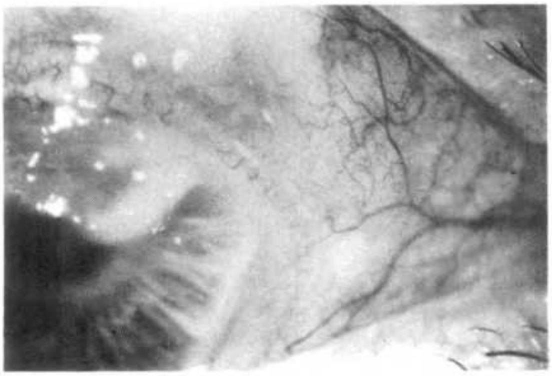

Fig. 5A

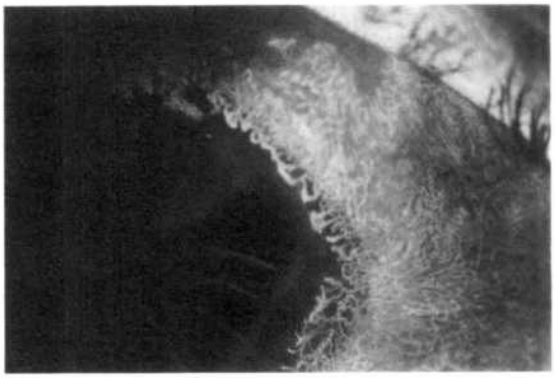

Fig. 5B

Figs. 5A, B Group 1B (A) *Corneascleral necrosis following a trabeculectomy operation.* (B) *Anterior segment angiograph in the same region. Late venous phase. The conjunctival capillary network fills normally except at 12.00, where there is total absence of any perfusion. The upper and lower parts of the gutter are vascularised, and there is poor or absent filling of the episcleral circle deep to the conjunctival network.*

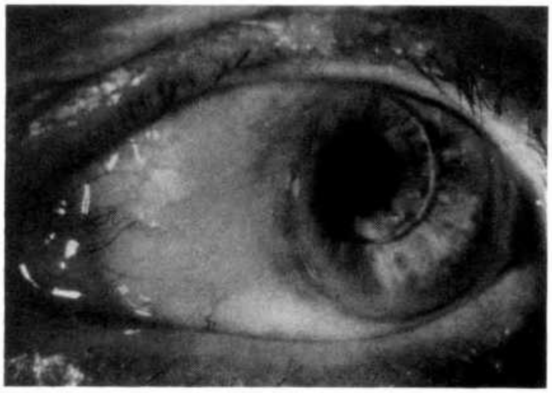

Fig. 6A

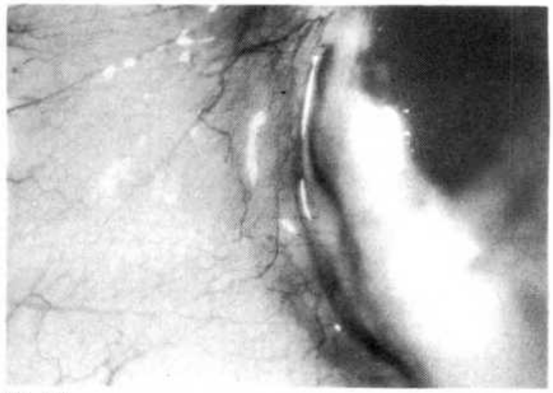

Fig. 6B

Figs. 6A, B Group 1B *Healed corneal gutter following treatment in a patient who developed sclerokeratitis following intracapsular cataract extraction and Federov pupil clip lens implantation.*

extent of scleritis. (2) The type and extent of the corneal changes. (3) The vasculature was documented by colour photographs and anterior segment fluorescein angiography. Particular attention was paid to the presence of vascular shutdown, flow patterns, and new vessel formation. (4) General condition: the presence of coexisting systemic disease or immunological evidence of this.

All the patients had scleral inflammation in one form or another but the patients were further divided into five groups according to the appearance of the corneal change and inspection of the anterior segment fluorescein angiograms (Table 1).

Group IA. Patients with corneal thinning, scleral inflammation, and vascular shutdown—idiopathic.

Group IB. Patients with corneal thinning, scleral inflammation, and shutdown—postsurgical.

Group II. Patients with corneal thinning, scleral inflammation, but with no vascular shutdown.

Group III. Patients with corneal infiltration, scleral inflammation, and vascular shutdown.

Group IV. Patients with corneal infiltration, scleral inflammation, but with no shutdown.

Table 1 Patients in each group

Group			*Patients*
IA	Corneal thinning Vascular shutdown	idiopathic	11
IB	Corneal thinning Vascular shutdown	postsurgical	8
II	Corneal thinning No vascular shutdown		2
III	Corneal infiltration Vascular shutdown		9
IV	Corneal infiltration No shutdown		15

GROUPS IA AND IB

There were 11 patients in group IA (23·9%) and eight in group IB (17·37%). Fluorescein in angiography in both groups revealed large areas of capillary shutdown both adjacent to and often away from the region of the corneal gutter. Figs. 1–8.

The eight patients in group IB all developed sclerokeratitis following surgery to the eye. Three followed routine intracapsular cataract extraction; one followed routine extracapsular cataract extraction with implant; one followed bilateral intracapsular cataract extraction but the affected eye had a leaking bleb; one followed a trabeculectomy done one month after a combined cataract and trabeculectomy in the fellow eye; one followed revisioning of an established trabeculectomy bleb; one followed a routine peripheral iridectomy. A localising cause was

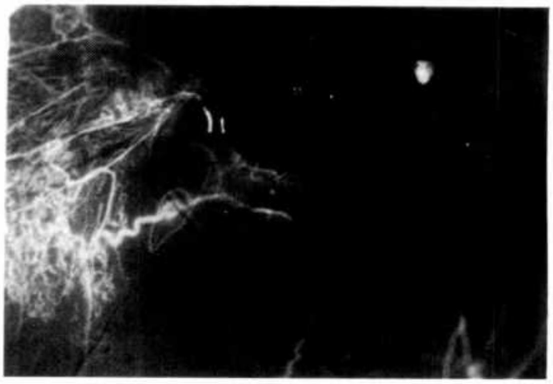

Fig. 7 Group 1B *Anterior segment fluorescein angiogram at the lower end of the gutter in a patient with a similar presentation to Fig. 6 which followed a simple, uncomplicated intracapsular extraction of cataract. There is a total occlusion of vascular network beyond the extent of gutter. All the visible vessels here are new vessels.*

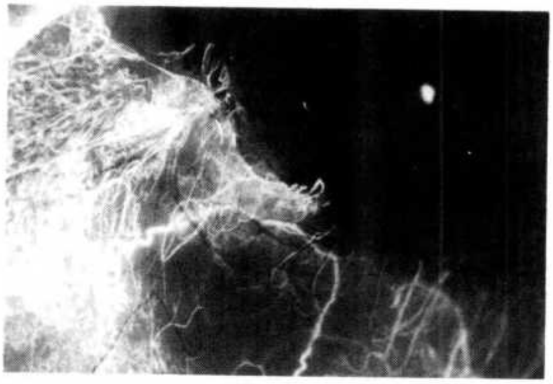

Fig. 8 Group 1B *Anterior segment fluorescein angiogram in the same patient as Fig. 7 taken three months later after treatment and in a quiescent stage. There is still no perfusion of the region beyond the gutter even at this late stage in the angiogram. It appears that once vessels have been occluded in this situation they do not recanalise.*

found in only one patient in group IA (the scleritis starting at a site of infection), but 83% of these patients had evidence of connective tissue disease.

Manifest connective tissue disease was present in six patients in the two groups (31·57%). Of these, three patients had rheumatoid arthritis (RA); three patients had Wegener's syndrome (one of whom had RA as well); five patients were in group IA; one patient was in group IB. All these patients with Wegener's granulomatosis had necrotising disease and two of the three patients with RA had necrotising disease.

Immunological changes. Ten of 11 patients in group IA had serological evidence of neurological abnormalities (90%); five of eight patients in group IB had abnormalities (62·5%); three patients had no serological immunological abnormality; one patient was in group IA and had severe RA and therefore can be presumed seropositive and has been included above; one patient was healthy in group IB and was probably normal. There were four patients with no serological abnormality (21% of both groups): three were in group IB; one was in group IA, and this was the patient whose lesions had an infective aetiology.

Uveitis. Cells and occasionally flare in the anterior chamber were noted during active stages of the disorder in seven patients (36·84%), but a definite attack of uveitis with synechia formation and keratic precipitates was documented in only four patients (21% of total). Three of these patients were in group IB. None of these patients with uveitis were seropositive (rheumatoid factor or antinuclear antibodies).

Of the types of destructive change found:

(1) *Peripheral corneal melting*—i.e., undermining of corneal edge, occurred in five patients in group IA and four patients in group IB.

(2) *Terriens-like*—i.e., sharply defined corneal edge occurred in five patients in group IA and four patients in group IB.

(3) *Keratolysis*—i.e., central and corneal thinning with or without peripheral changes occurred in one patient in group IA.

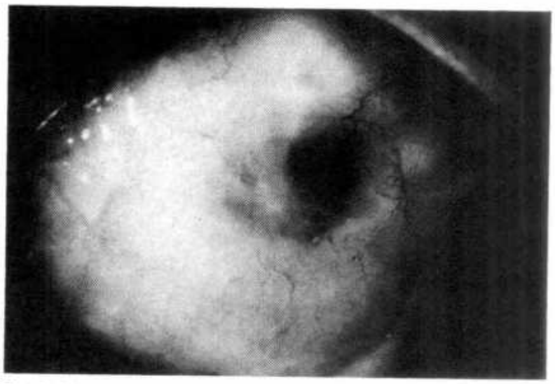

Fig. 9 Group III *Sclerosing keratitis in a man with longstanding diffuse anterior scleritis.*

Corneal vascularisation was present in eight patients in group IA and six patients in group IB (i.e., total of 73·68%).

Of the scleritis present, in group IA four patients had diffuse scleritis (36·36%) and seven patients had necrotising scleritis (63·6%). In group IB two patients had diffuse scleritis (12%), one patient had nodular scleritis (25%), and five patients had necrotising scleritis (62·5%).

GROUP II

Corneal gutter scleral inflammation, *no* vascular shutdown. Only two patients fulfilled the criteria, and, of these, one showed gross vascular anomalies but no perfusion problems.

GROUP III

Nine patients fell into this category (19·5%) (Figs. 9–11).

Corneal changes. All the patients showed an immune response, that is, a precipitin ring either at the edge of the lesion or spreading into the cornea. A variety of other non-specific changes were also noted, such as lipid deposition, limbal infiltrates, and oedema.

Corneal vascularisation was present in all patients (100%).

Of the *scleritis* present four patients had diffuse (44%), three had nodular (36·33%), and two had necrotising (22%) scleritis.

Manifest connective tissue disease. No patient

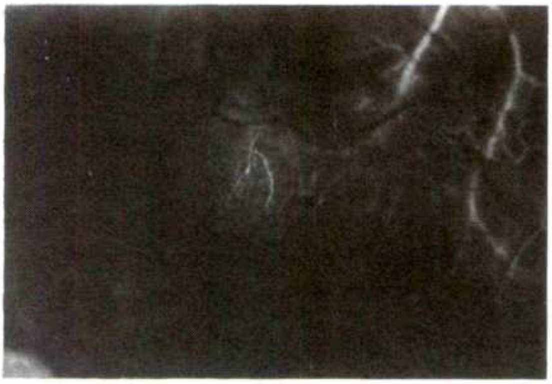

Fig. 10A

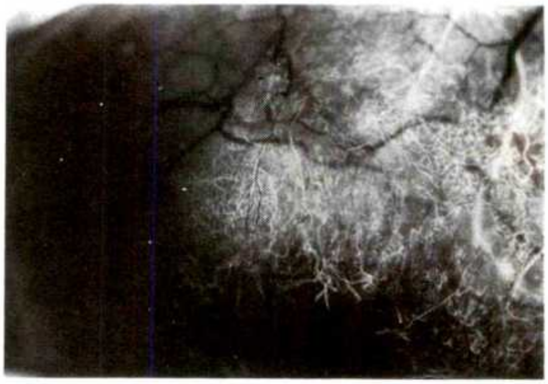

Fig. 10B

Fig. 10A, B Group III *A patient with a similar corneal appearance to Fig. 9. The deep perforating arteries fill fast and normally, but the deep episcleral plexus fails to fill. The sclerosing keratitis at the limbus contains numerous new vessels.*

in this group had any manifest connective tissue disorder.

Immunological changes were present in eight patients (88·8%).

Uveitis. One patient had definite uveitis and was seronegative (11·11%).

GROUP IV

Corneal infiltration, scleral inflammation, no shut-down in angiography: there were 15 patients in this group (32·6%).

Corneal vascularisation. Only eight patients showed the presence of vessels (53·3%).

Scleritis present. Twelve patients had diffuse (80%) and three had nodular (20%) scleritis (one with early necrosis).

Immunological changes. Twelve patients showed some changes, but in a few this was evident only during disease activity (80%).

Manifest connective tissue disease was present in only three patients (20%): one had RA and Sjögrens syndrome, one had ulcerative colitis (UC), one had Crohn's disease and arthritis (one patient also had congenital syphilis and one patient had orbital Wegener's granulomatosis).

Uveitis. A uveal reaction was reported in 11 patients but a definite uveitis documented in seven patients (46·66%). Five of these patients were seronegative (71·4%).

Discussion

Anterior segment fluorescein angiography has been found to be helpful in scleritis to differentiate patients who have vascular occlusive changes[1] requiring intensive systemic steroid therapy for its control from those who have normal vascular patterns and who respond well to non-steroidal anti-inflammatory

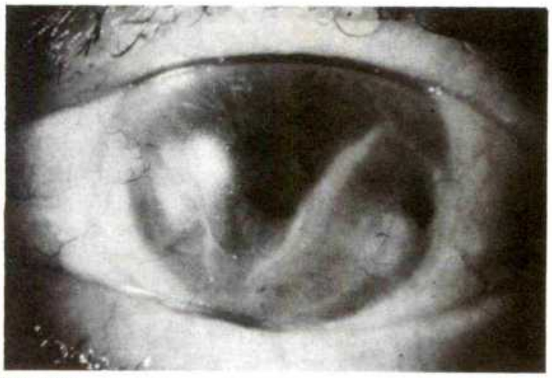

Fig. 11A

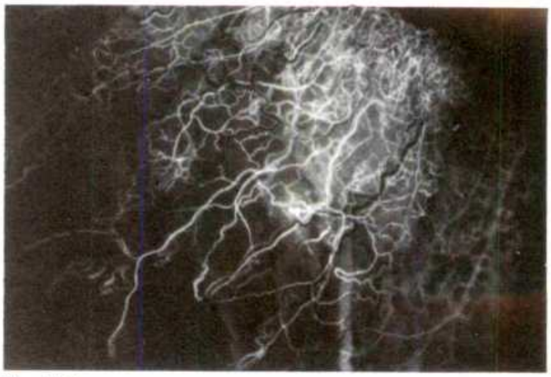

Fig. 11B

Figs. 11A, B Group IV *Lipid infiltration at the limbus following recurrent attacks of sclerokeratitis.* (A) *Anterior segment fluorescein angiogram at 8.30. The limbus is normally perfused at a very high rate of flow; the whole vascular network being filled within 3 seconds of the appearance of the dye.*

therapy. This paper evaluates the use of this technique in the investigation of those who, in addition to scleral inflammation, also have corneal changes.

Corneal changes are observed in approximately one-third of those patients who have scleral disease. It has been known for many years that there are two major types of corneal change in scleral disease,[2] namely, that in which the cornea becomes opaque and vascularised and that in which various forms of absorptive change of the cornea exist. This absorption can vary from an aggressive infiltrative and destructive keratolysis involving the peripheral cornea or complete corneal melt to a slowly progressive thinning of the peripheral cornea which may take many years.

Examining both the corneal changes and the fluorescein angiograms which were taken during the course of the disease, we found that five almost distinct groups could be identified depending on the type of corneal change (infiltration or thinning) and whether or not there was evidence of vaso-obliteration of the episcleral or limbal vessels. In the group in which there was both vascular shutdown and corneal thinning two further subgroups emerged, because it became obvious that the corneal changes had been precipitated by surgery to the eye. Immunological examination of these patients revealed that 60% of them had some immunological abnormality, though only one had manifest connective tissue disease (rheumatoid arthritis). By contrast, 90% of the other group (so called idiopathic) had serological abnormalities, and 45% of them had manifest seropositive connective tissue disease (rheumatoid arthritis, Wegener's granulomatosis, or periarteritis nodosa). There was no difference in the types of corneal thinning or vascularisation or scleral disease between the two groups. All these patients with Wegener's granulomatosis and two of the three patients with rheumatoid arthritis had necrotising disease. Two of the three patients with Wegener's granulomatosis and one with polyarteritis nodosa showed destructive changes which transgressed the limbus.

It would seem therefore in this group that both types have the same characteristics in that there is a 'vasculitis' of the episcleral and limbal vessels which leads to vascular shutdown which in turn leads to catabolic resorption of the stromal tissue. If the systemic disease is severe, then the destructive changes occur spontaneously or, as in the case of one of these patients, as a result of intercurrent infection.

Patients who have a systemic vasculitis but with an apparently normal eye can be shown to have areas of vascular occlusion or non-perfusion. If such a patient had an eye operation, or if there were circulating immune complexes, these would be precipitated at the site of surgery and an autoimmune response could be induced. In the postoperative group of patients 60% had some serological evidence of immunological abnormality, and such a mechanism might be the cause of the corneal destruction. It is noticeable that those who have problems after surgery tend to develop a scleritis if the sclera is disturbed by surgery (trabeculectomy or retinal detachment) and a corneal thinning if they have a cataract extraction with corneal section. The part that any intercurrent infection plays in this process is unclear, and it was not possible to detect any obvious infection in this postoperative series, but the notes almost always indicated that the eye had been continuously irritable following surgery. Uveitis occurred only in the one seronegative patient.

It was extremely unusual to find corneal thinning or melting without vascular shutdown (group II), and one of the two patients in this group was later known to have developed shutdown. The other patient, however, seemed to be similar to the patients in group I, so this change remains unexplained.

By contrast, even though the scleral disease was severe, vascular occlusive changes were much less common in patients who developed corneal infiltration as opposed to corneal thinning and the vaso-obliterative changes were much more patchy. Eight of the nine patients who showed shutdown had immunological abnormalities, but none had manifest connective tissue disease. Again uveitis occurred only in the seronegative patients. Necrotising disease is, as would be expected, rare in this situation.

The group who showed corneal infiltration without vascular changes also contained the largest number of patients with seronegative arthritis and with uveitis, which again occurred only in seronegative patients.

It would appear therefore that scleral thinning or destruction occurs when there is obliteration of the episcleral network of vessels. The series indicates that this is a result of an immunologically induced vasculitis regardless of whether the patient has manifest connective tissue disease or not. The other forms of corneal infiltration, though often the result of a local immune response, are not necessarily associated with permanent vascular occlusion and are much more likely to occur in seronegative patients. Uveitis in patients with sclerokeratitis has been found only in seronegative patients.

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Management of unsuccessful lacrimal surgery

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SUMMARY Two hundred and eight cases of failed dacryocystorhinostomy presenting to the Lacrimal Clinic at Moorfields Eye Hospital between 1970 and 1985 were reviewed. All cases underwent a further operation. The reasons for failure were usually apparent on reoperation. The surgical technique is described. A second dacryocystorhinostomy is a highly successful technique that spares both patient and surgeon the lifelong commitment to a bypass tube.

Professor Barrie Jones concluded in a paper given before the Ophthalmological Society of the United Kingdom in 1973 that if one adheres to certain basic principles in both dacryocystorhinostomy (DCR) and canalicular surgery, 'it is possible to achieve, in a high proportion of cases, an accurate and large anastomosis of sac to nasal mucosal wall, or of canliculus to sac to nose, with a very high rate of permanent success, leaving only a small minority of cases that are best dealt with by less satisfactory intubational procedures which require continuing aftercare.'[1]

The failure of dacryocystorhinostomy is rare, occurring in most series in less than 10% of cases.[2-7] The management of unsuccessful DCR poses a therapeutic problem. Some authors recommend the insertion of a Lester Jones bypass tube,[8] which, despite its usefulness, necessitates a lifetime of continuing aftercare. Procedures directed at the ablation of tear production are to be discouraged, as most of them can cause a dry uncomfortable eye and may occasionally pose a threat to vision.[9-11]

Secondary surgery on the lacrimal drainage system, if performed with attention to the principles stressed by Professor Jones, is likely to be successful in a high proportion of cases. Our initial results with this technique were reported in 1973.[12]

From 1970 to 1985, 204 patients have presented to the Lacrimal Clinic at Moorfields with symptoms attributed to a non-functioning dacryocystorhinostomy and undergone secondary DCR surgery. Four patients had bilateral failed dacryocystorhinostomies. The purpose of this communication is to describe our technique and present the results of this further surgery. The patients were also examined retrospectively to determine what factors were responsible for the failure of the primary operation.

Patients and methods

In addition to a history the preoperative assessment included a dye test, syringing, slit-lamp and intranasal examination, and diagnostic probing. Contrast studies[13] were performed in the majority of patients; this essential investigation was omitted in patients who could not co-operate or in those with large regurgitating mucoceles. The *x*-ray findings were most helpful in planning the secondary procedure. In those patients with a large sac remnant, whether completely obstructed or partially patent, as in the sump syndrome (Fig. 1), the reoperation consisted in identifying the anterior aspect of the previous rhinostomy in the first instance, enlarging it anteriorly, and if necessary in all directions, to find virgin nasal mucosa. In the presence of a canalicular obstruction or where there was only a small remnant of sac (Fig. 2) it was essential to identify the junction of the sac and common canaliculus before isolation of the rhinostomy site. Dissection and identification of the common canaliculus as an initial step are technically easier when the medial tissues are fixed to the rhinostomy and immobile.

At the time of operation the appropriate procedure was performed by a technique described more completely below. Possible reasons for failure of the primary operation were noted.

After discharge the day after operation patients were seen one week postoperatively, at six weeks, and again at three months. Canalicular tubing, if introduced, was removed three months later. The

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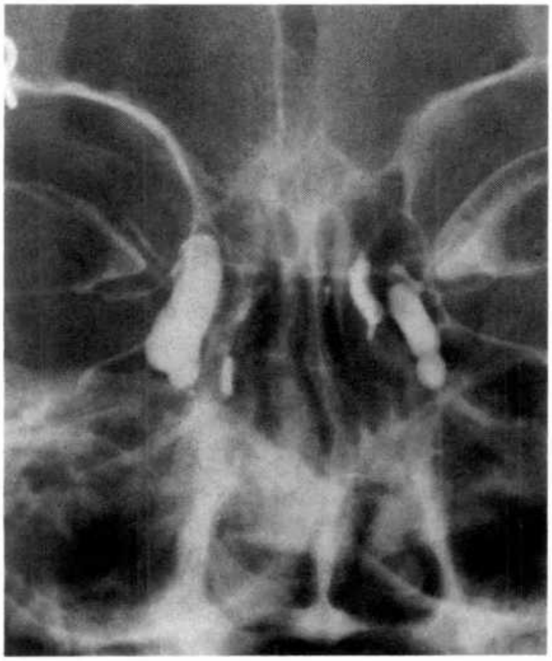

Fig. 1 *DCG. Bilateral sump syndrome following failed lacrimal surgery. Contrast enters nose; also partially retained within large sac remnant.*

patients were seen subsequently five to six months postoperatively, and a dye test was repeated. The absence of symptoms and a positive dye test were construed as evidence of success. Some patients with symptoms of watering only in adverse climatic conditions and who had positive dye tests were also considered successful, but grouped separately. A failure was defined as any patient with a negative dye test that had symptoms.

TECHNIQUE OF REOPERATION

Operations in adults are carried out under hypotensive anaesthesia, when possible.[14] In children and adults in whom hypotension is contraindicated, lignocaine 1% with adrenaline is infiltrated locally for haemostasis.

A skin incision is made through the original scar. Orbicularis is separated at the junction of orbital and palpebral portions by a technique of traction stitches previously described.[1]

If a dacryocystogram has shown a canalicular obstruction or a small sac to be present, probes are passed into the canaliculi. The medial palpebral tendon, if present, is divided (Fig. 3). Beneath the cut tendon canalicular tissue is sought lateral to the sac in the tissues of the medial lid. A combination of sharp and blunt dissection is used to separate the scar above and below the probes (Fig. 4). Great care is taken not to enter the lumen of the canaliculi. When the probes can be seen and easily felt within the canaliculi, attention is directed to defining the anterior edge of the original rhinostomy.

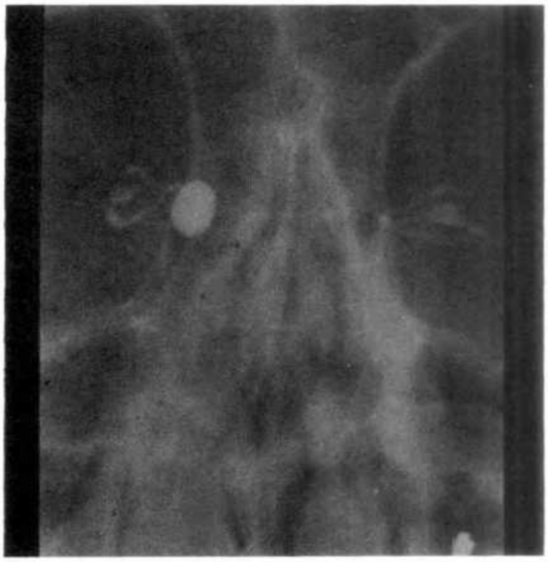

Fig. 2 *DCG. Common canalicular obstruction following failed lacrimal surgery. Note contralateral mucocele.*

Periosteum is freed from bone for approximately 4 mm anterior to the bony edge of the original rhinostomy (Fig. 5). The nasal mucoperiosteum is then separated from the front edge of the rhinostomy, to which it is usually adherent, by means of a Traquair periosteal elevator. This manoeuvre usually provokes bleeding. The bone is removed approximately 4 mm anteriorly, and may be enlarged inferiorly and superiorly, to expose virgin nasal mucosa (Fig. 6).

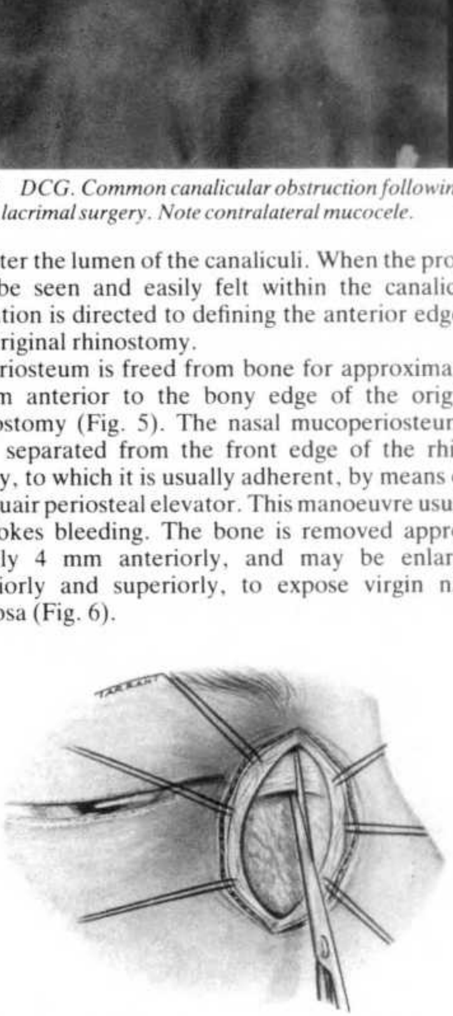

Fig. 3 *Operative. Medial palpebral tendon divided if present. Canaliculi sought in tissue beneath it. Traction sutures to orbicularis and deep tissues aid exposure. Right eye.*

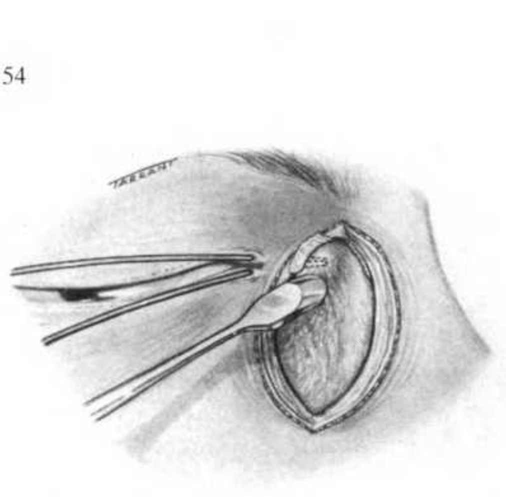

Fig. 4 *Operative. Junction of common canaliculus with remaining lacrimal sac exposed by blunt dissection with probes in canaliculi.*

A trapdoor incision based in the newly exposed virgin nasal mucosa is cut so that the lateral free edge is close to the previously identified common canaliculus and the upper and lower edges are adjacent to the edges of the newly enlarged rhinostomy (Fig. 6). If a large sac remnant exists and the canaliculi are not isolated, the trapdoor incision may be made at the site of the old anastomosis. The flap is reflected anteriorly with traction stitches (Fig. 7). The interior of the rhinostomy is then inspected.

At this stage the reason for the original failure of the original DCR may become apparent. Bone, ethmoid air cell, turbinate, non-absorbable sutures, stones, or scar may be present and must be removed (Fig. 7A).

If the common canaliculus is obstructed, an incision is made lateral to the obstruction to expose healthy canalicular mucosa (Fig. 7B). All intervening scar tissue is excised and healthy canalicular mucosa is then anastomosed to the remaining sac or the nasal mucosa. Canalicular flaps should be sutured under slight tension so that they do not adhere internally and obstruct. All canalicular obstructions are intubated and the tubes secured within the nose (Fig. 8).

Anterior and posterior mucosal flaps are created and sutured with fine absorbable suture material such as 6/0 Dexon (Fig. 9).

Orbicularis and tendon are repositioned with an absorbable suture, and the skin is closed with an interrupted nylon suture.

Results

Of the 204 patients studied 137 were female and 67 were male. Four patients had bilateral failed DCRs. There were 102 left eyes and 106 right eyes, giving a total of 208 cases.

The average age of the patients at onset of the original symptoms was 39 years and at initial surgery was 42 years. The interval from initial surgery to reoperation averaged 5 years. Follow-up ranged from 3 months to 10 years and averaged 15 months.

One hundred and sixty-three patients complained of tearing. Forty patients had residual discharge with pressure on the lacrimal sac. The primary procedure was a DCR in 150, a DCR with tubes in 45, and a canaliculo-dacryocystorhinostomy (CDCR) in 7, while 6 patients had a dacryocystectomy. One hundred and forty-seven patients had had a single procedure prior to presentation, 54 had had one unsuccessful secondary procedure elsewhere, and seven patients had had more than one unsuccessful secondary procedure.

Of 154 DCGs available for review, a common canalicular obstruction was noted in 101 cases, a dilated sac in 29 cases, a dilated sac with overflow into the nose (sump syndrome) in 12, and blockage at the site of the rhinostomy in 12.

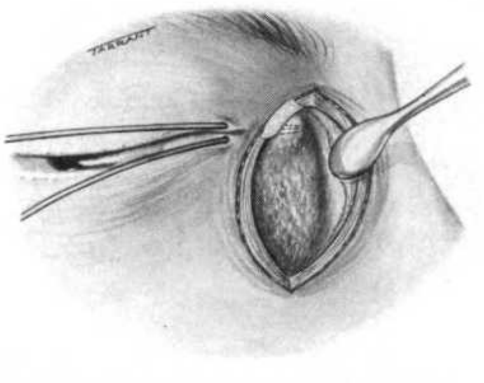

Fig. 5 *Operative. Bone at anterior edge of previous anastomosis identified, and periosteum stripped anteriorly.*

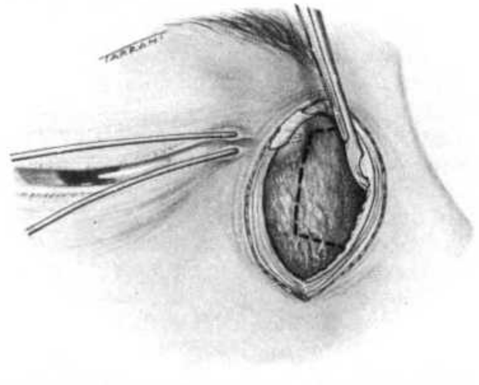

Fig. 6 *Operative. Bony rhinostomy enlarged.* (Dotted lines: *approximate location of trapdoor incision).*

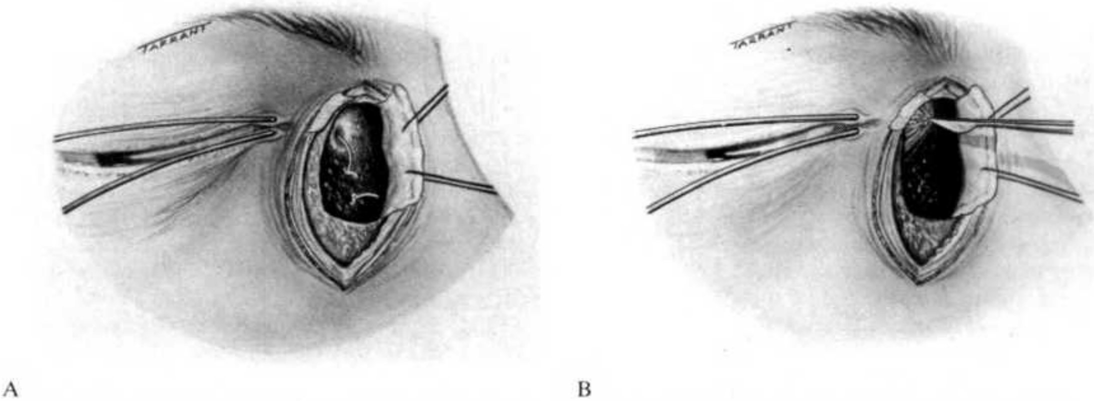

Fig. 7 *Operative. Flap reflected forward using traction sutures. Interior of rhinostomy inspected. At this time reasons for failure often become evident. Possible findings on inspection include:* (A) *Non-absorbable suture or scar in relation to common canaliculus, or* (B) *membranous scar over internal common opening, which can be incised with sac knife guided by ends of lacrimal probes. For other possible findings see text.*

Type of surgery. Of the 208 cases 37 DCRs, 127 DCRs with intubation of the canaliculi, and 44 CDCRs with anastomosis of canalicular remnants to the nasal mucosa were performed.

Results of surgery. Of the 208 secondary operations performed 176 were successful (85%). Ten patients were dry following surgery with positive dye tests, but admitted to moisture in the cold and the wind. Therefore 186 patients had successful secondary surgery (89%).

Of the 22 patients who had unsuccessful secondary operations 15 consented to have a third operation. Of these 15 patients 13 were cured of tearing. Therefore the success of a third operation was 87%, essentially the same as for the primary procedure. With a third operation 96% of the cases operated on were cured without recourse to a bypass tube.

REASONS FOR FAILURE

The presumed cause of failure of the primary operation(s) are depicted graphically in Table 1.

Errors in ostium location or bone removal. One hundred and eleven errors in ostium location were noted. In eight cases the ostium was located too posteriorly, in 10 cases it was too anterior, in 25 too

Table 1 *Reasons for failure of primary operation*

Reasons for failure	*No. of patients*
Inappropriate size or location of ostium	111
Common canalicular obstruction	108
Scarring within rhinostomy	28
Intervening ethmoid	15
Sump syndrome	10
Active systemic disease	7
DCR to air cell	6
Three of above	36

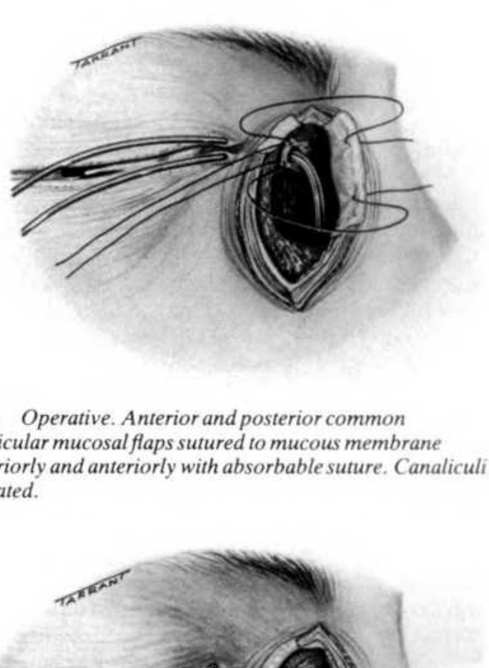

Fig. 8 *Operative. Anterior and posterior common canalicular mucosal flaps sutured to mucous membrane posteriorly and anteriorly with absorbable suture. Canaliculi intubated.*

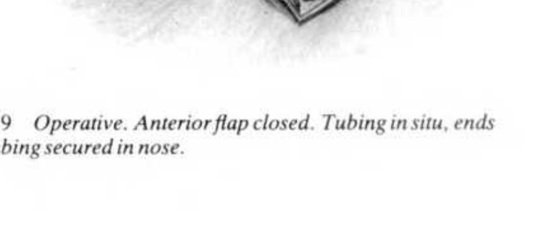

Fig. 9 *Operative. Anterior flap closed. Tubing in situ, ends of tubing secured in nose.*

high, and in 24 too low. Ethmoids were found in direct relation to the opened and scarred sac in 15 cases. Intervening loose bone was found within the scarred sac in an additional 18 cases. No bony ostium was detected at all in 19 cases. Many cases had a combination of these errors in bone removal and ostium location: a posteriorly placed ostium, for example, might have had the remains of an ethmoid air cell within the rhinostomy.

Common canalicular obstruction. Common canalicular obstruction was seen in 108 cases. In 26 of these patients canalicular obstruction occurred in conjunction with an associated inflammatory process within the sac, and in 39 patients bone was seen in close proximity to the obstructed internal opening. Three patients had scarring, with non-absorbable suture found against the common opening. Two patients had sarcoid involving the sac and common canaliculus.

Scarring within the anastomosis. Sac scarring was the only abnormality seen at surgery in 17 cases. Both small obliterated and obstructed sacs and normal sized sacs filled with chunks of fibrous tissue were observed: the large majority of these cases examined histologically showed non-specific inflammation and fibrous tissue. In 11 cases non-absorbable sutures were observed in the midst of the scar and were thought to have provoked the scarring, either directly or indirectly as a result of infection.

Of note is that, of the 15 cases that failed secondary surgery, 93% were thought to have failed because of exuberant scarring. One patient underwent unsuccessful surgery four times: no mucosa was available and on each occasion scar filled the anastomosis. This patient required a bypass tube.

Persistent mucocele and sump syndrome. In all 29 cases of persistent mucocele a failure fully to open the sac and duct into the nose was noted. Ten patients had a sump syndrome diagnosed on the basis of their DCG findings. A typical DCG is seen in Fig. 1. Eight of these patients had bone remaining medially within the nasolacrimal canal.

Other findings. Several cases showed evidence of an incomplete or anatomically unsound procedure. In one case an anastomosis had been made to the maxillary antrum. In six cases the anastomosis had been incorrectly made between lacrimal sac and an ethmoid air cell. In nine cases an adequate bony rhinostomy was found, but either the sac, or the nasal mucosa or both appeared not to have been opened.

Two cases of congenital lacrimal fistula undiagnosed prior to the original surgery were corrected by methods described elsewhere.[15] Two cases with multiple unremoved sac stones were found. In six cases no obvious cause for initial failure was found.

Discussion

In 1921 Dupuy-Dutemps and Bourguet described a technique of external dacryocystorhinostomy modifying Toti's operation.[16] They emphasised the importance of making an anastomosis of sac to nose with sutured mucosal flaps.

This procedure has undergone surprisingly few modifications over the past 65 years. The success rate has improved, however, owing to the introduction of modern anaesthetic techniques, the use of fine suture materials and needles, as well as the availability of soft plastic stents. There have also been recognisable advances in the diagnosis and treatment of canalicular disease, made possible by macrodacryocystography and microscopic surgery of the common canaliculus. These techniques, pioneered by Professor Barrie Jones, reached a level of refinement whereby, in a series of 100 of his DCRs, a success rate of 99% was achieved.[17]

Since the initial descriptions of this operation surgeons reporting on many large series have modified the technique and examined the reasons for failure in the patients in whom DCR did not result in relief of symptoms.[2-7 12 15] The occurrence of scarring within the anastomosis in the patients who were reoperated on is common to all these series.[2-7 12 15] The failure rate due to scarring in some series, particularly the more recent ones, is alarmingly high.[6 7]

This finding may be partly attributed to an emergent trend in lacrimal surgery that pays too little attention to careful suturing of flaps. It is often not enough, and never adequate, simply to punch a hole in the nose and line it with tubing in the hope that mucosa will grow round it before a fibrous scar can form. It is a basic principle of general surgery that tissues should be repaired when possible by primary rather than secondary intention. Massive granulation and scarring, secondary haemorrhage and infection from unapposed mucosal flaps, and the inefficient passage of tears through scar rather than through a mucosa lined orifice can be the result.

The scarring that was observed in 128 patients in this series fell into two types. A localised common canalicular scar, perhaps the result of persistent sac disease following the primary operation, was seen in 111 cases. Dense scarring within the anastomosis was observed in 17 cases. In all cases but one case mucosa was found anterior to the rhinostomy of the original operation and used to recreate an anastomosis whose goals were to incorporate the common canalicular opening completely into the nose, and to create a mucosa lined drainage apparatus with the careful suturing of flaps. One case that had no available mucosa underwent four unsuccessful procedures, but eventually a Jones tube was required. A secondary intention technique with extirpation of sac and nasal mucosa at the time of primary operation doomed to failure all attempts at reoperation.

Some authors have noted that bone regrowth is occasionally responsible for failure of the primary operation.[4,6] Others maintain that bony regrowth does not occur and that fibrous tissue is primarily responsible for obstructions at the site of the bony ostium.[5] In our series 19 cases had no bony ostium at the time of secondary surgery. The bone and mucosal surfaces in these cases appeared as though no previous rhinostomy had been performed. A larger percentage of children were seen to have 'reformed' ostia at the time of reoperation (24%) than adults (6%). Because bone growth is more rapid in a growing child, the contention of bone regrowth cannot altogether be excluded. However, if a mucosal edge-to-edge anastomosis was performed at the primary operation, it is highly unlikely that bony regrowth could proceed across an established tissue plane. This emphasises further the control on outcome exerted by mucosal end-to-end suturing.

Pure ostium problems were presumed to be the cause of failure in 52% of cases in this series. An ostium that is too low may not bypass a mid or upper sac obstruction; an ostium that is too high forces tears to defy gravity and leaves the nasolacrimal duct as a blind pouch vulnerable to reinfection. The ideal ostium, in our view, should remove all bone between the medial wall of the sac and the nose, leaving approximately 5 mm around the canaliculus free of bone. Thus, following DCR, the sac and duct should cease to exist as anatomical structures and be incorporated instead into the nose.

Persistent mucoceles were seen because of a failure to attain this goal completely rather than from any obscure infection. Either the bone or the mucosa of the lacrimal duct, or both, were observed not to have been adequately marsupialised into the nose.

Other causes for DCR failure that have been recognised include conjunctivitis,[2,4] septate sacs incompletely connected to the nose,[3] bone within the rhinostomy and intranasal adhesions,[3] and canalicular problems.[6,7,12,15] The last can be minimised by preoperative recognition, care in manipulation of the canaliculi, and deliberate inspection of the internal opening at the time of surgery. Additional causes for failure seen in this series included chronic inflammation from non-absorbable suture in relation to the internal common opening, operations that connected sac to ethmoids or other sinuses, sarcoid, interference of the middle turbinate, and undiagnosed congenital lacrimal fistula.

The success rate for a second DCR is about 85%. The reoperation may be repeated, if necessary, with the same success rate as the one that attends initial reoperation. Thus reoperation can cure a significant proportion of failed dacryocystorhinostomies. These patients will be spared recourse to a permanent indwelling Pyrex appliance. In addition, if the primary operation is performed on the basic surgical principle of edge-to-edge anastomosis as described by Dupuy-Dutemps and Bourget and as emphasised by Professor Jones, the need for secondary surgery may diminish.

We thank Terry Tarrant for providing the illustrations, Dr Glynn A S Lloyd for arranging the DCGs, and Carol A Sausser, registered nurse, for her aid in the compilation and recording of data.

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Clearing the cataract backlog

SIR JOHN WILSON

From IMPACT: an International Initiative against Avoidable Disablement

One of many invaluable contributions which Professor Barrie Jones has made to international action for the prevention of blindness is that he so often found the apt phrase to express its objectives. At one of the earliest meetings of the International Agency he defined that objective as 'eliminating the over-burden of avoidable blindness'. That was later quantified to mean reducing the prevalence to not more than 0·5% of the population in any country and not more than 1% in any community.

During the 1960s surveys revealed the formidable scale of that 'over-burden', associated with cataract in the Indian subcontinent, with trachoma in the Middle East, with onchocerciasis in West Africa, and with that complex of malnutrition and infection which was later identified as xerophthalmia. The Indian figures revealed that 40% of the blindess was due to cataract, and for some years it was assumed that this phenomenon was peculiar to the Indian subcontinent. Later surveys in East Africa, in the Western Pacific region, and more recently in Latin America have revealed very similar figures, between 35% and 45% of the blindness due to cataract, and, though the most spectacular figures are in Southern Asia; it now seems likely that an excessive prevalence of cataract will be found in any underserved, deprived community where it is possible to identify blindness among upper age groups.

At the outset the World Health Organisation was reluctant to include cataract as one of the priorities of the global programme for the prevention of blindness. It was argued that trachoma and xerophthalmia are preventable at the level of primary health, that onchocerciasis can be controlled by an environmental intervention, but that cataract, being curable but not preventable, could not logically be included in a preventive programme. Such pendantry was soon swept away by the flood of statistics and cataract was included as one of the four main priorities of the global programme.

Eye camps

In 1960 the Royal Commonwealth Society for the Blind, in collaboration with Indian ophthalmologists who had pioneered techniques of mass treatment in rural areas, began a process of upgrading the administration, surgical supervision, and aftercare in 'eye camps' which, at the time, were looked upon with understandable reserve by surgeons accustomed to more orthodox city practice. In 1969 the society launched the Eyes of India campaign, in which we invited partners throughout India to collaborate in organising mass treatment projects for cataract and to identify the major causes of rural blindness. That campaign—co-ordinated by a remarkable, blind, Indian administrator, Dr Rajendra Vyas—led on to the Indian national programme for the prevention of blindness launched a few years later on the personal initiative of Mrs Indira Gandhi. One of the objectives of that programme is to clear the backlog of cataract, which is estimated to cause the blindness of at least six million people in India.

Last year over 900 000 cataract operations were performed in India. Most of these operations were in rural camps, and, if the figures in Pakistan and Bangladesh are added, the total number is well in excess of 1 million. The Royal Commonwealth Society's programme in India involved camps in more than 2000 villages where 180 000 cataract operations were performed at a unit cost averaging £5–£6.

The word 'camp' perhaps gives a misleading impression of the scale of organisation and quality of treatment which is now possible in such projects. The small village camp, performing perhaps 40 cataract operations, ideally serves the needs of a single community, but much larger camps are now regularly organised involving impressive resources of a whole township: transport, multiple operating centres, thousands of daily meals, and a small army of volunteers.

In a 'disability camp' organised by the Government of India during the launching of the IMPACT programme in 1983 the 'camp'—preceded by the screening of 40 000 potential patients—consisted of a tented township organised round a well equipped State hospital. Eighty Indian visiting specialists joined with local doctors in performing some 12 000 operations, mostly for cataract but also with orthopaedic and ENT interventions.

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A mobile unit can range in size from a single vehicle to what is virtually a mobile hospital with a fleet of transport and comprehensive equipment. Sometimes, as in Pakistan and East Africa, supplies are sustained by a light aircraft.

Unprecedented expansion

The cataract backlog must be seen in the intimidating perspective of population growth in developing countries. Over the next 40 years the population of those countries is expected to double, but the number of people over 55 years of age will quadruple. Dr Carl Kupfer has estimated that in India, in order to reduce the accumulation of some 6 million people now blind by cataract and to keep pace with the 1–1½ million new cases each year, the number of operations performed annually must be in the region of 3 million. If the same arithmetic is applied to other mass population countries of Asia and Africa, a vast surgical need is revealed, implying unprecedented expansion in the whole base and concept of the ophthalmic profession.

Ideally cataract operations should be performed only by a fully qualified ophthalmic surgeon. However, the number of patients is so great and the number of surgeons is so few that to insist on that principle everywhere would exclude the possibility of clearing the backlog. Fortunately it has been possible to approach this question not in terms of absolute principle but in relation to the degree of training and supervision necessary to achieve a safe cataract operation. In Bangladesh, with the help of ophthalmologists from Australia, general practitioners have been trained in a six-month course to undertake cataract surgery in rural areas. With their addition to the eye camp programme the number of cataract operations in that country has more than doubled over the last four years. In Kenya specially trained clinical officers, working with the mobile units, perform cataract operations. A rigorous review undertaken by the International Eye Foundation concluded that the work of these officers compared favourably with that of ophthalmic surgeons working in similar conditions. Specially licensed auxiliaries also undertake cataract operations in Fiji, Vietnam, and parts of China.

If it is possible to have a 'bottleneck' connected to a 'backlog' then the bottleneck in most eye camps is the time patients remain in the camp after treatment. The operation takes about 10 minutes, the convalescence from seven to 13 days. We have resisted the temptation to use lens implants because of the complications which might occur when a patient returns to a remote rural village. Consideration is now being given to whether, with improved operating procedures with more sutures, it might be possible safely to reduce the convalescent period to two days, thus opening the possibility of at least doubling the number of operations in each eye camp. Subjecting this traditional system to operational analysis must be done in such a way as not to destroy its spirit of improvisation and community involvement.

On the plains of India camps are suspended during the hot summer months. In areas where there is a regular demand for surgery small eye hospitals are being built to continue the work throughout the year.

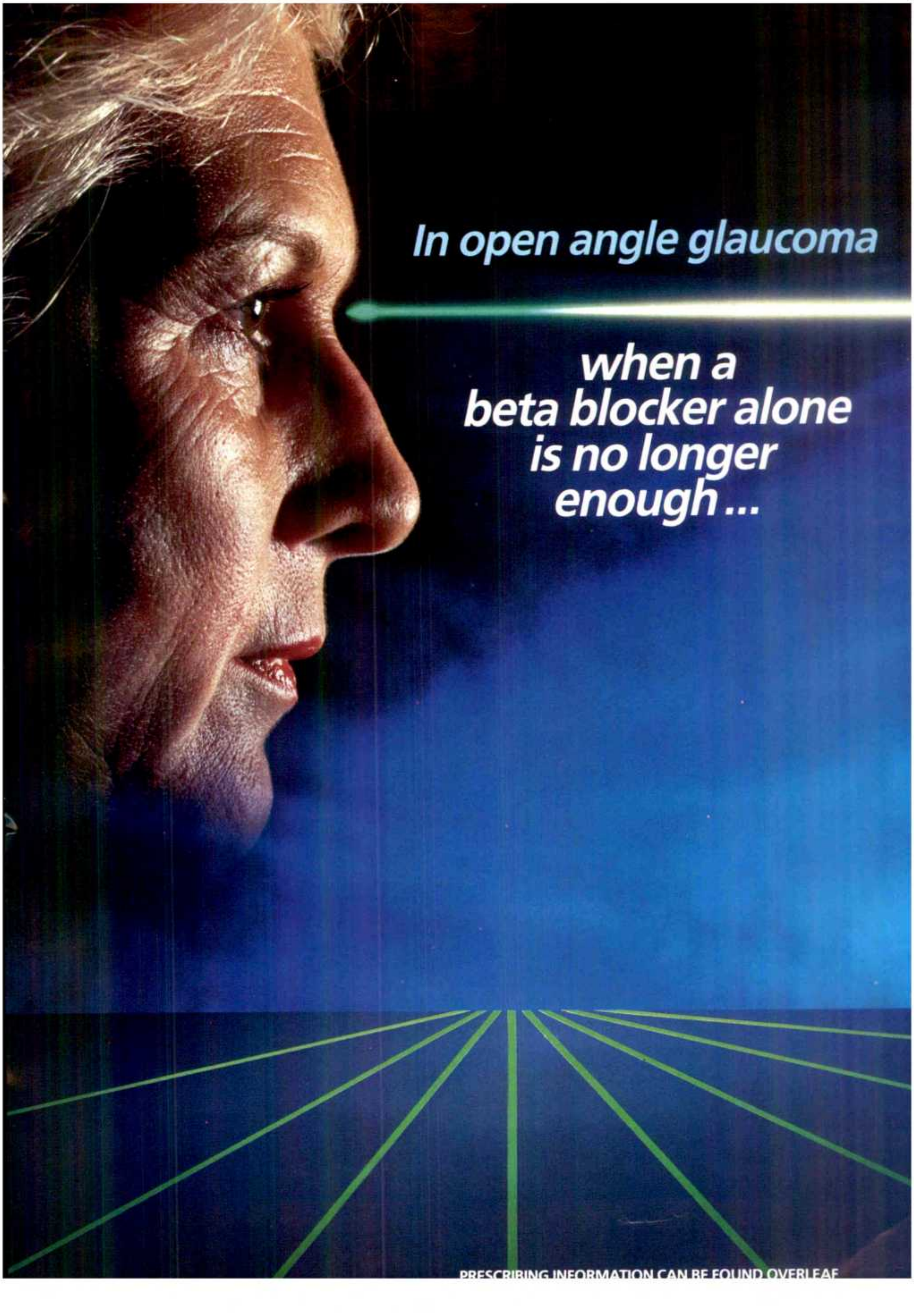
The national programme in Thailand is particularly interesting because of its determination to clear the cataract backlog without creating a special 'vertical' structure for that purpose. It is estimated that there are 500 000 blind people in Thailand (1·14% of the total population) and that 47% of the blindness is due to cataract. District hospitals—there are more than 450 of them serving a rural population of 44 million—have the responsibility for case finding and postoperative care of cataract patients, who are referred for operation to 75 regional hospitals.

In a Thai district of 100 000 population there are likely to be from 250 to 400 cases of blinding cataract. With over 80 eye specialists now practising in rural areas, compared with 20 five years ago, the expectation is that by the year 1995 the anticipated backlog of 400 000 cases of curable cataract will have been cleared and, at the same time, the country's surgical capacity will have increased to deal with the anticipated 50 000 new cases each year. Under this system the unit cost of the cataract operation, convalescence, and spectacles is estimated at $20, approximately £14.

Not only cataract

It is increasingly being recognised that the cataract backlog can no longer be treated in isolation. When the IMPACT programme was launched in Thailand last December, it was estimated that there are at least 300 000 deaf people in the country who could have a measure of hearing restored by middle ear surgery followed by amplification. Among orthopaedically handicapped people there are at least 200 000, mostly victims of poliomyelitis, who could have movement restored by surgery and prosthetic aids. Similar figures are being recorded in many other countries representing a disability backlog of such monstrous proportions that it must constitute one of the major challenges over the next decade to the health services of developing countries. The disablement lobbies in many countries, increasingly aware of the medical possibilities, are understandably demanding that the disabled in this generation have a right to remedial surgery.

Perhaps we too readily assume that this is a problem only for the developing countries. At the national seminar on the prevention of disablement, held at the Royal Society in London in February 1986 it was estimated that cataract is the cause of blindness for 8000–10 000 of the registered blind of the United Kingdom. Many of these patients may have complicating factors but a majority could probably benefit from surgery. In some areas, particularly in the South of England, the waiting time for a cataract operation can be from three to four years. Perhaps we could do with an eye camp in Sussex.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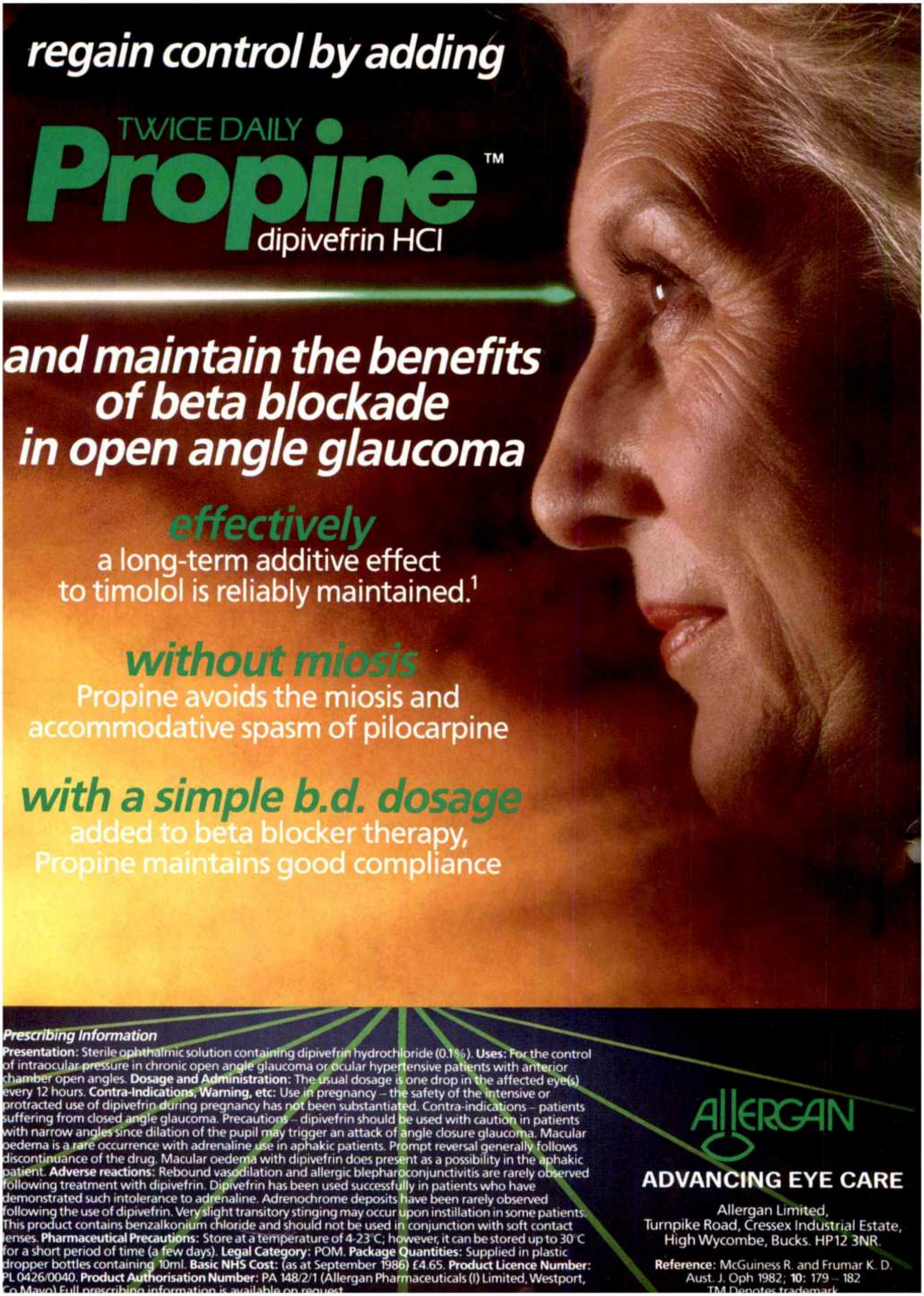

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Effect of osmolarity of artificial tear drops on relief of dry eye symptoms: BJ6 and beyond

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SUMMARY Patients with clinically well defined keratoconjunctivitis sicca (KCS) participated in two trials of hypo-osmolar tear substitutes. The trials were double masked, single crossover studies with computer generated random order allocation and were conducted by postal questionnaire. In the first trial a hypo-osmolar formulation using polyvinylpyrrolidone and hydroxyethyl cellulose was compared with the patients' usual treatment (BJ6 or hypromellose) and found to be inferior, especially in respect of blurring and stickiness caused by higher viscosity. In the second trial hypo-osmolar preparations of BJ6 and hypromellose were compared with their iso-osmolar equivalents and found not to be significantly different in their effects. Hypo-osmolarity alone does not seem to guarantee relief of symptoms in KCS. Other factors including viscosity and colloid osmotic pressure may be more significant.

Keratoconjunctivitis sicca is a well recognised cause of much ocular pain and irritation, and, although many different solutions have been suggested as tear replacements, no single formulation has been shown to be superior for relief of symptoms. Attempts have been made to modify the composition of artificial tear drops to give maximal relief of dry eye symptoms, and some broad principles have emerged, especially relating to pH.[1-3] Recent studies have suggested that increased tear osmolarity is responsible for the symptoms, signs, and possibly the epithelial changes seen in keratoconjunctivitis sicca.[4-8] Tear diluents have been suggested as a form of treatment and a small study carried out to show possible benefit.[9] The present study was designed to assess whether drops with lower osmolarity but identical pH would give greater symptomatic relief in KCS.

Material and methods

TRIAL DESIGN

Two trials of hypo-osmolar tear substitutes were carried out. Patients with proved KCS who had been followed up for a minimum of six months in the External Diseases Clinic were selected. Diagnosis was based on history, symptoms, and signs including tear film abnormalities, rose Bengal staining, and grossly deficient Schirmer test (<5 mm) on multiple visits. Exclusion criteria were stringent, and all patients using preservative-free drops or requiring them less often than four times daily as well as those with cicatrising conjunctival disease, epithelial metaplasia, or specific types of postinflammatory corneal pathology were excluded. The trials were double masked, neither doctor nor patient being aware of which preparation was in use or in which order, with a single crossover after two weeks' treatment with each drop. The drops were posted to the patients with a questionnaire designed to allow evaluation of immediate or later effects on a wide range of symptoms commonly experienced in KCS as well as any untoward effects.

The two treatment groups were equivalent in sex, age, and treatment prior to the trials. The ratio male/female was 1/4 and the mean age 51 years. The patients had previously been using hypromellose or BJ6 in a ratio of 3/1.

MATERIALS

For the first trial a new hypo-osmolar drop was formulated using two polymers different from those in our usual artificial tears but similar to many commercial preparations and previously found to be acceptable thickening agents[10] (Table 1).

When the results of the first trial were known it was

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Table 1 *Hypodrops Mk 1*

Polyvinylpyrrolidone	0·5%
Hydroxyethylcellulose	0·5%
Sodium bicarbonate	0·4%
Potassium chloride	0·025%
Chlorhexidine acetate	0·01%
Distilled water to	100%
pH≈8·4	
Osmolarity≈135 mosm/l by freezing point depression	
Colloid osmolarity approximately equal one to another	

decided to create hypo-osmolar formulations of the usual artificial tear substitutes BJ6 and hypromellose to allow closer comparison (Table 2 and 3).

Results

Twenty-nine patients took part in the first trial using Hypodrops Mk 1 versus their usual drops of either BJ6 or hypromellose. Twenty-six questionnaires were completed and returned. Of these, two were spoiled and unusable, two gave no preference, and of the remainder 17 (77%) preferred their old drops and only five the new ones. There was no difference between the groups in the sex ratio, order of drops used, type of symptoms usually experienced, or specific effects on symptoms, but 6/17 complained of blurring and 5/17 of stickiness while using the new drops.

These complaints appeared to be related to an increased viscosity of the new drops compared with the old, and preference for the old drops was significant at 1–5% by Fisher's test.

Table 2 *Hypodrops Mk 2 (hypromellose)*

Hypromellose		*Hypodrop HM*
0·45%	Sodium chloride	—
0·37%	Potassium chloride	0·37%
0·19%	Sodium borate	0·19%
0·19%	Boric acid	0·19%
0·3%	Hydroxypropylmethylcellulose	0·3%
0·1%	Benzalkonium chloride	0·01%
Distilled water to 100%		
pH≈8·4		
Osmolarity≈158 mosm/l by freezing point depression		
Colloid osmolarity approximately equal one to another		

Table 3 *Hypodrops Mk 2 (BJ6)*

BJ6		*Hypodrop BJ6*
0·6%	Sodium chloride	0·15%
0·45%	Sodium bicarbonate	0·45%
0·25%	Hydroxypropylmethylcellulose	0·25%
0·01%	Chlorhexidine acetate	0·01%
Distilled water to 100%		
pH≈8·4		
Osmolarity≈160 mosm/l by freezing point depression		
Colloid osmolarity approximately equal one to another		

The second trial involved 26 patients of whom 24 returned usable completed questionnaires.

The overall preferences expressed were: iso-osmolar 14, hypo-osmolar 6, undecided 4. The apparent preference for iso-osmolar drops was not significant at the 5% level.

Despite the random allocation of the drops there was an apparent first use effect on expressed preference. Of those who preferred the hypo-osmolar drops all six had used the hypo-osmolar preparation first. Of those preferring the iso-osmolar drops nine (60%) had used the iso-osmolar first and only five (33%) the hypo-osmolar. Again these findings were not statistically significant.

Replies to specific questions concerning relief of common dry eye symptoms and possible adverse effects of the drops showed no statistically significant difference for the two preparations (Table 4).

Discussion

KCS is essentially a symptomatic problem complicated in a few patients by infection, for which there is still no completely satisfactory treatment. Replacement of the missing fluid from the outer eye would seem a simple matter, but despite clinical and laboratory studies[11] no universally acceptable tear substitute exists. Even though alkaline eye drops give the best subjective relief for KCS sufferers, only hypromellose and BJ6 are alkaline. Among other commercial preparations values as low as pH 4·6 are found, and none has a value higher than pH 7·50.[12] Unfortunately the symptom complex caused by tear deficiency is not specific, and many other outer eye disorders, especially blepharitis and primary ocular surface disorders, may produce identical symptoms. It follows that the large number of prescriptions for artificial tear drops therefore only partly represent replacement therapy for dry eyes and probably the greater use is as a placebo. This more than any other factor explains the conflicting reports of their efficacy, and it was considered essential in this study to try the drops only in those patients with well

Table 4 *Effect on symptoms*

Iso-osmolar preferred	*Symptoms*	*Hypo-osmolar preferred*
63% (9)	Stickiness	67% (4)
36% (5)	Stinging	67% (4)
29% (4)	Burning	50% (3)
93% (13)	Grittiness	100% (6)
63% (9)	Blurring	50% (3)
43% (3)	Itching	67% (4)
50% (7)	Pricking	83% (5)
29% (4)	Pain with TV	33% (2)
50% (7)	Smoke related pain	67% (4)

Differences not statistically significant established KCS who were dependent on tear substitute drops.

Increased osmolarity of the tears in the marginal tear strip has been found in patients with KCS[4,5] and proposed as a useful diagnostic procedure.[13] The test involves microsampling of the marginal tear meniscus and estimation of osmolarity by freezing point depression. The tear osmolarity from normal eyes averaged 302 (SD 6·3) mosm/l, and tears from KCS eyes averaged 343 (SD 32·3) mosm/l. With a cut-off at 311 mosm/l, the samples differentiated with a specificity of 93·7% and a sensitivity of 94·7%. There was a large variability between right and left eyes, and the reproducibility was not good, so considerable doubt must remain about the validity of microsampling of marginal strip tear fluid in eyes with reduced flow, altered mixing, and enhanced evaporation.

Individual and diurnal variations in tear osmolarity have been found in normal, healthy, asymptomatic adults with individual subject means ranging from 310 to 334 mosm/kg.[14] The finding of increased tear osmolarity in patients with dysthyroid eye disease[15] also casts doubt on the prime role of hyperosmolarity in the causation of the epithelial changes seen in KCS. Although damage to rabbit corneal epithelium in vivo and in vitro has been demonstrated after exposure to solutions of hyperosmolar concentrations in the same range as is found in KCS, these rabbits do not show the clinical signs of KCS, and evidence of epithelial damage was found only at ultrastructural level. Cells showed loss of microvilli and desmosomal attachments, tending to round up or desquamate.

Hyperosmolarity of the tear fluid has been observed in rabbits after occlusion of the ducts of the tear producing glands, and the model has been suggested as a good one for the study of KCS.[16] These animals do not show any of the clinical features of human KCS, and the relevance of this experimental animal model to human disease has still to be confirmed. There is also a need to collate the findings in the proposed rabbit model with the previously reported finding of different osmolarity in rabbit tear fluid from the conjunctival sac and that obtained by cannulation of the lacrimal excretory duct. It was postulated that tears in the conjunctival sac remain isotonic, with plasma-like concentrations of sodium and chloride at all flow rates because of transport of these ions across the conjunctiva.[17] Why this does not occur in the rabbit dry eye model and in human subject remains unexplained.

Tear diluents have been proposed for treatment of KCS, and it has been shown that solutions of low osmolarity (75 mosm/l) are irritant and the ability of any hypo-osmolar solution to reduce tear fluid osmolarity is very short lasting.[9] The reported benefit of 150 mosm/l drops with a 2:1 preference for hypo-osmolar drops has not been confirmed in our present study. It may be relevant that, among the small treatment groups, three out of four were not using artificial tear drops regularly, and so despite the osmotic evidence of KCS they could not be said to be typical dry eyed patients. The studies we now report suggest that differences of osmolarity do not override the effects of viscosity or pH and that when these latter are controlled no clear preference for hypo-osmolar drops can be shown.

A recent publication has drawn attention to the possible effect of total colloidal osmolarity, or oncotic pressure, on the efficacy of artificial tear drops.[18] Although the colloidal osmolarity of normal tears and most tear substitutes is low, one commercial preparation said to be useful because it is hypo-osmolar was found to have an oncotic pressure 60 times greater than that of most other artificial tear drops. The high colloidal osmolarity of the preparation is attributed to the high content of non-ionic crystalloids, especially glucose. The drops used in the trial now reported contained matching amounts of macromolecules to give comparable colloid osmolarity.

Further studies are planned to determine whether increased colloid osmolarity with or without alkaline pH will offer greater symptomatic relief. Meanwhile, although there will always be considerable individual variations of preference for one of the many tear substitutes available, there do not at present seem to be any good clinical data to suggest a need to modify the formulation of BJ6 or hypromellose to relieve dry eye symptoms.

We are grateful to Mr V Andrews and the staff of the Pharmacy for much help in formulating the drops and to Professor F J Holly for measurements of colloid osmolarity.

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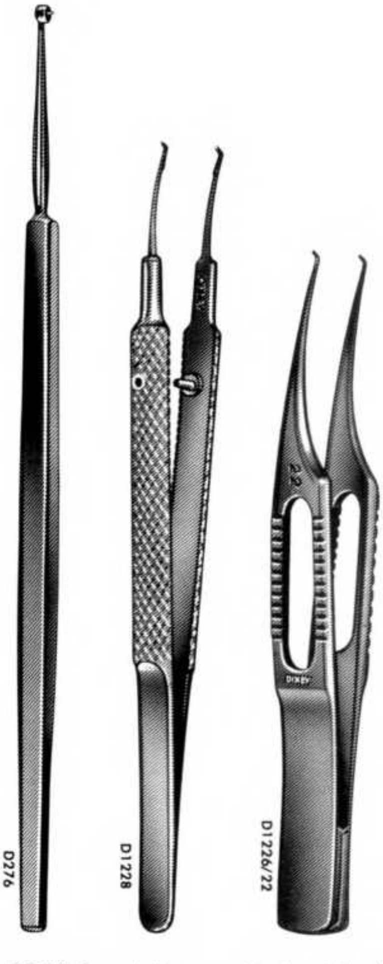

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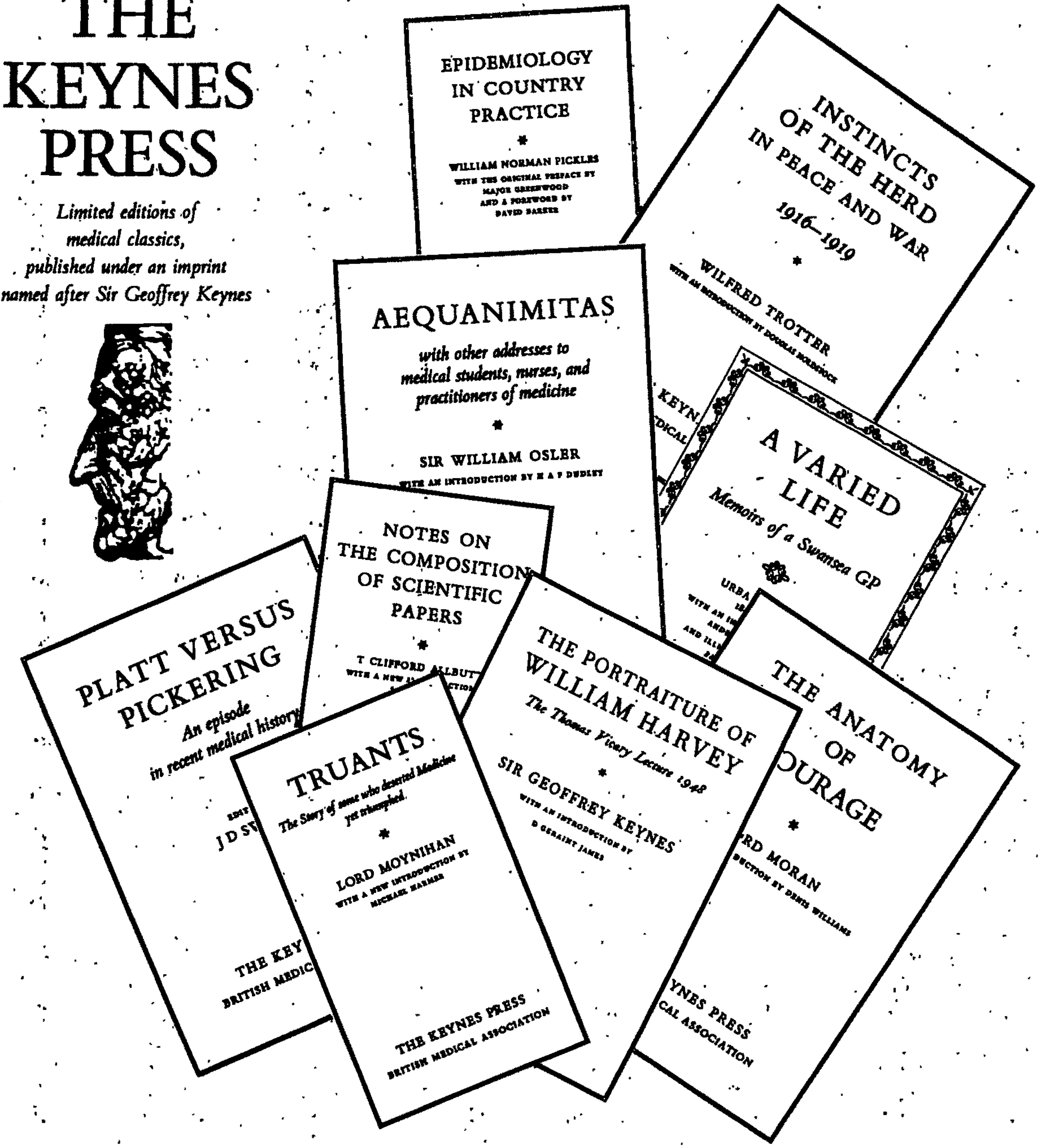
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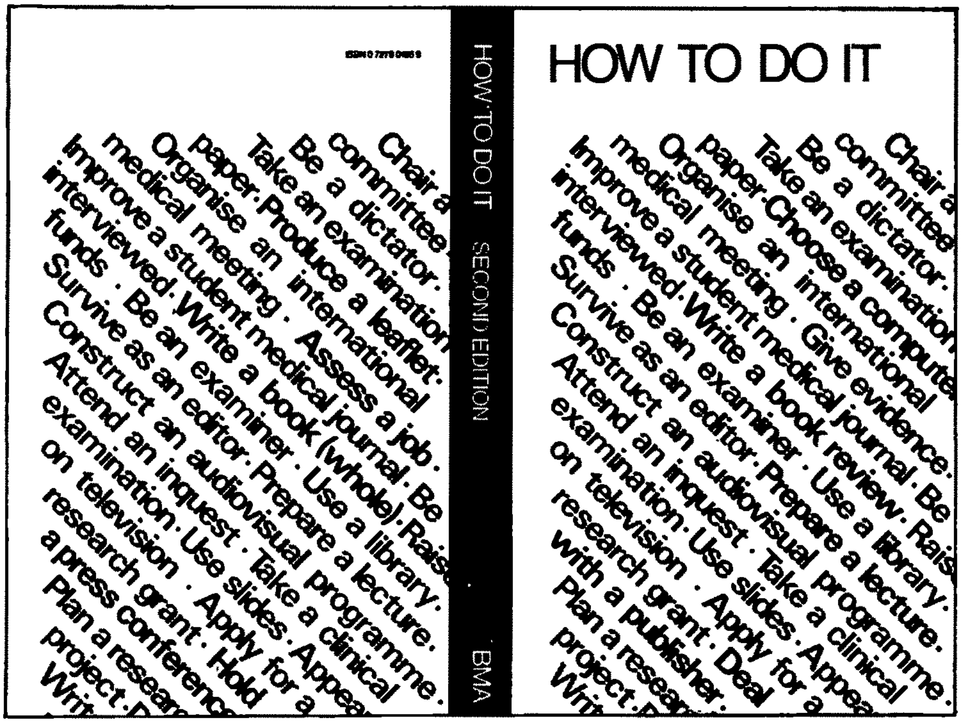

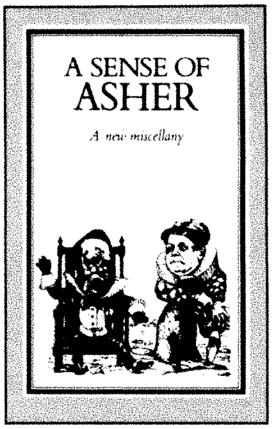

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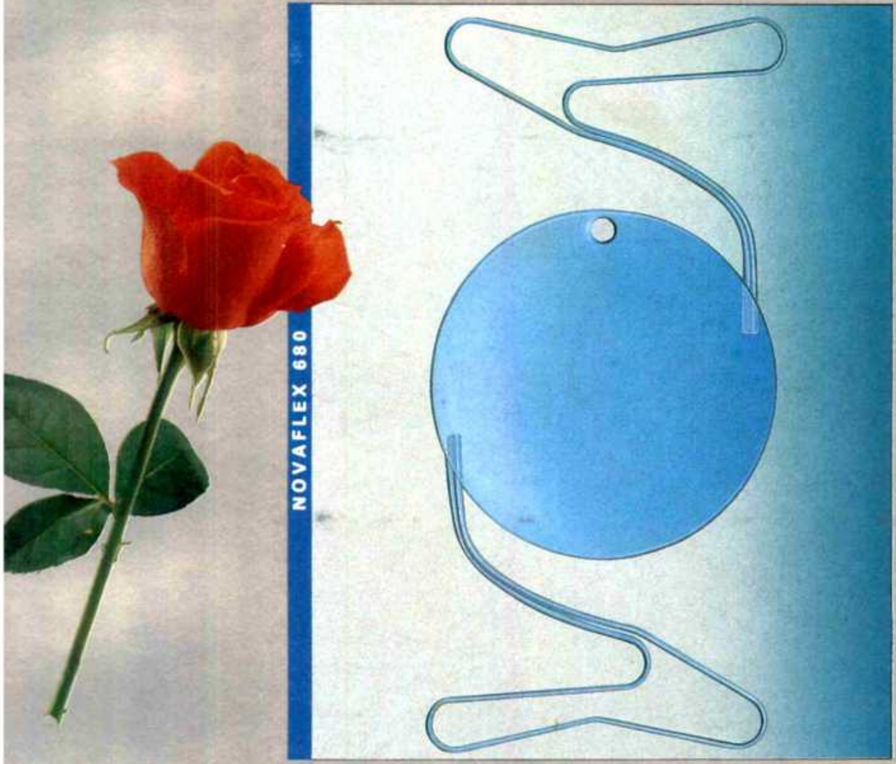

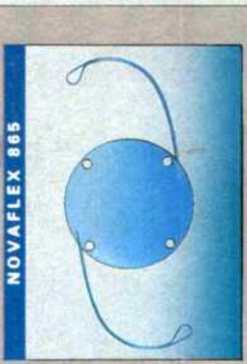

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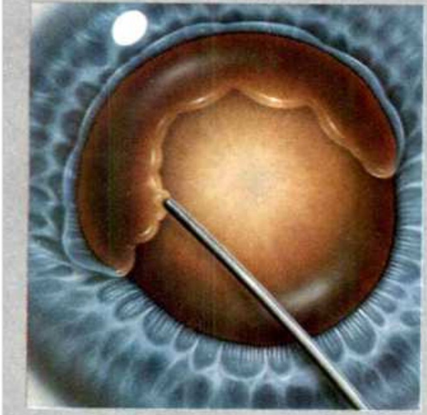

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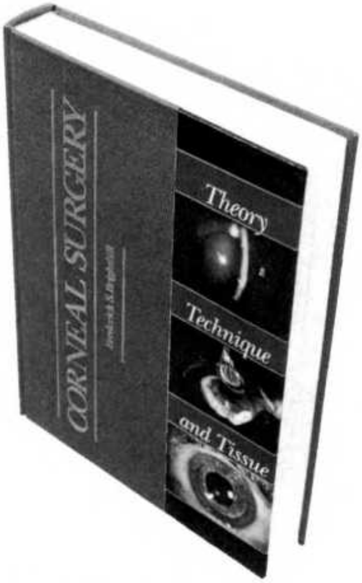

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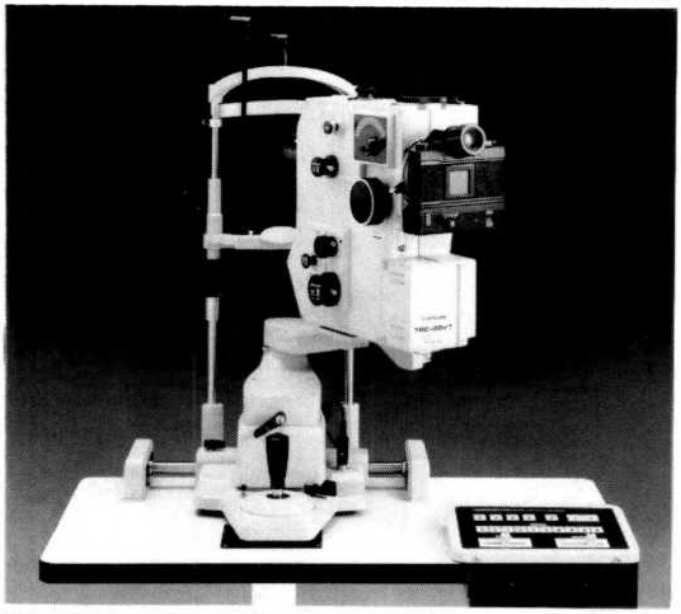

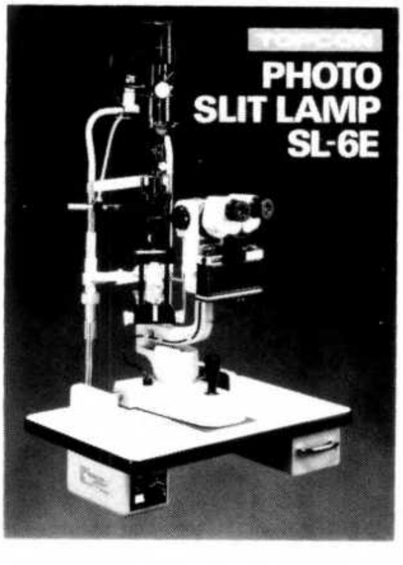

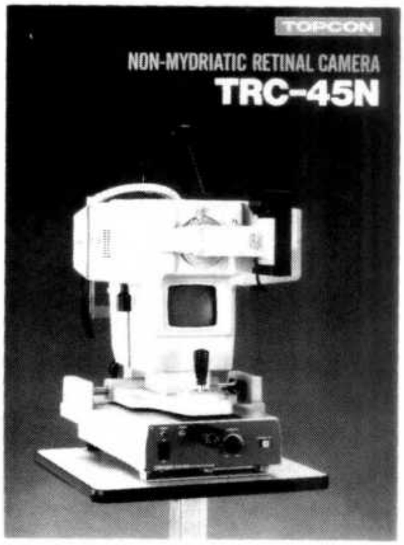

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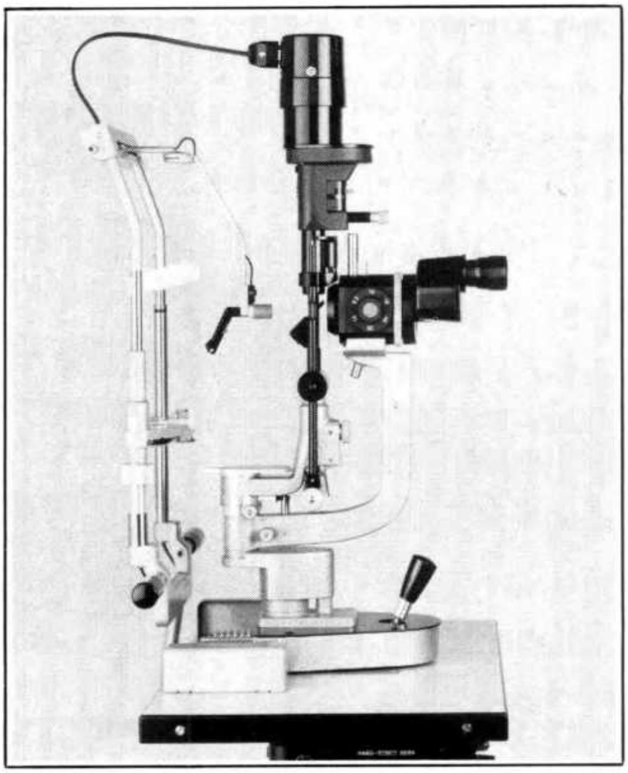

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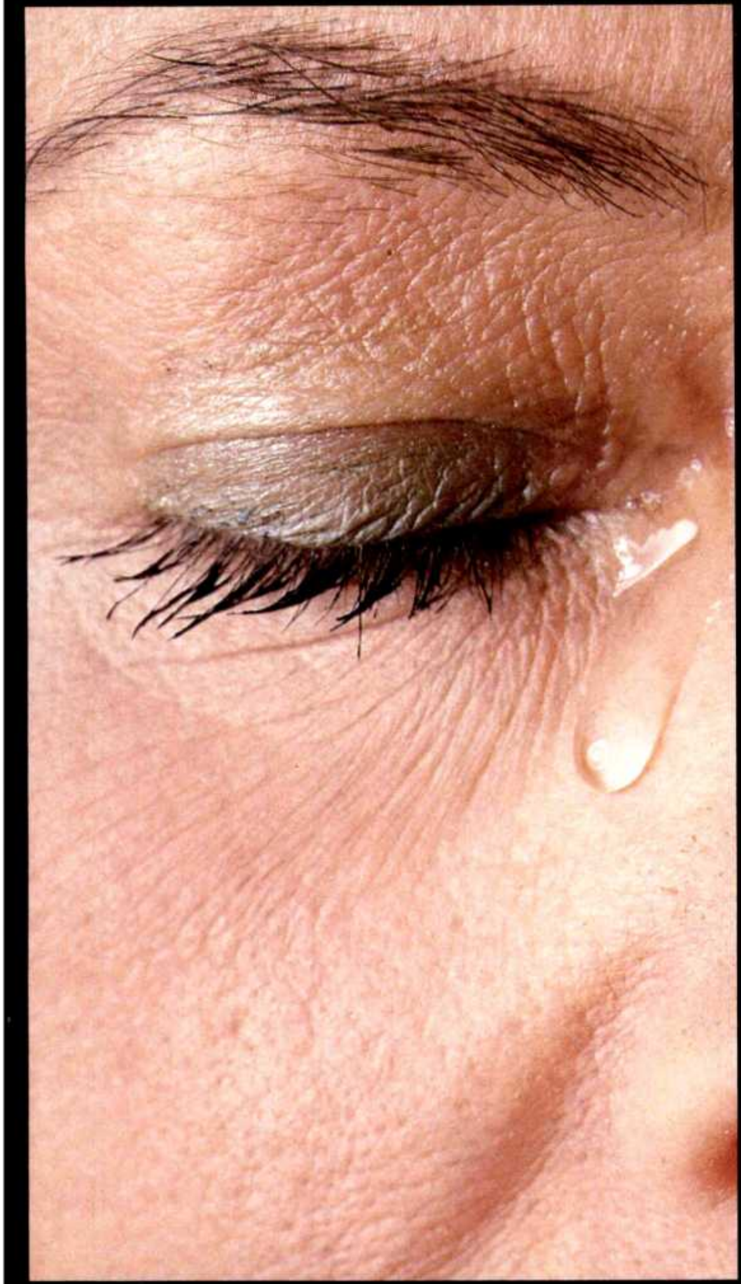

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British Journal of Ophthalmology, 1987, **71**, 165

Editorial: Abnormal PERG

We can hardly be expected to be experts in all aspects of ophthalmology, and nowhere is this more true than in the field of electrodiagnostics. There must be only a mere handful of practising ophthalmologists who understand the niceties of the subject. It is a pleasant surprise, therefore, to see a paper in this issue of the *BJO* which is not only easily understandable but appears to be a real advance in the subject, enabling, as I see it, a clear distinction to be made between macular and optic nerve disease.

The author, Dr G Holder, reminds us that there is good evidence of a receptor and inner nuclear site of generation of the conventional flash ERG, whereas the pattern evoked response PERG probably arises in the region of the ganglion cell layer. A simplistic view of the situation would be that the former is a predominantly receptor cell response to a crude stimulus, whereas the PERG, requiring a degree of integrated neural activity for its appreciation and response, is in fact being processed, as it were, nearer to the brain. Putting it crudely, one might say that the flash was just a stimulus but the pattern was a message.

The present paper explains with great clarity two principal components of the PERG, a positive component at about 50 ms and a negative at about 95 (called respectively P50 and N95). It was found that the P50 component showed abnormalities where retinal or macular dysfunction occurred, but in optic nerve disease the N95 component was mainly involved. This seemed to support the view that the N95 component might be generated in the region of the ganglion cells, being affected in optic nerve disease by retrograde degeneration.

It has to be admitted that the average clinician during his ordinary working day gives little thought to electrodiagnostic testing, regarding it as something esoteric and not of much practical value except perhaps to unmask malingerers or predict retinitis pigmentosa. In fact, of course, the potential of this field of study of the visual functions is enormous. We may find before long that electronic studies of function begin to take a more important place in our clinical examination than the familiar but admittedly inaccurate subjective studies of visual acuity and visual field. Thus from being a somewhat rarified laboratory exercise it now seems possible that the electrodiagnostic mode of study of visual function might in the end give us accurate objective data as to the quantity, quality, and location in the field of visual function together with the possibility of identifying the exact anatomical location of any malfunction.

As I mentioned at the beginning of this note, it was really delightful to read a paper on what it has to be admitted is a fairly esoteric subject and to be able to understand it and enjoy it. Our journal cannot have too many such papers. RJHS

British Journal of Ophthalmology, 1987, **71**, 166–171

Significance of abnormal pattern electroretinography in anterior visual pathway dysfunction

G E HOLDER

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SUMMARY The pattern electroretinogram (PERG) findings in 72 patients with disease of the anterior visual pathways are presented in relation to the site of dysfunction. Two components of the PERG are described which are selectively involved in different pathologies. In particular, the main positive P50 component is invariably affected in retinal/macular dysfunction, whereas the late negative N95 component is principally affected in optic nerve disease.

The pattern electroretinogram (PERG) is becoming increasingly used in the investigation of patients with anterior visual pathway disease, as it may enable a functional assessment of the retinal ganglion cells. Absent or reduced PERGs in the presence of intact flash ERGs have been described in three cases of optic neuritis,[1] in a case of glaucoma,[2] and in a patient with optic atrophy following traumatic optic nerve damage.[3] These findings were in keeping with the experimental work of Maffei and Fiorentini,[4] subsequently confirmed by Hollander *et al.*,[5] who had demonstrated that the PERG in the cat gradually disappeared over a four-month period following optic nerve section while the flash ERG was essentially unaffected. Histological examination at that time showed degeneration of the ganglion cells with minimal preganglionic damage. These results have been taken to indicate that the ganglion cell layer is implicated in the generation of the PERG, whereas it is known that the conventional flash ERG arises in the receptor and inner nuclear layers of the retina.

More detailed reports of PERGs in optic nerve or macular dysfunction have subsequently appeared,[6-15] but there has been disagreement among these authors as to whether the PERG is consistently affected in optic nerve disorders. Indeed some authors[16 17] have concluded that the PERG has no or little value in the assessment of patients with suspected optic nerve disease. Similarly, no definite conclusions as to the site of PERG origin have been reached.

This report reviews the PERG findings in 72 patients in whom the PERG was abnormal and in whom a diagnosis has been established. The results are presented in an attempt to elucidate further the possible diagnostic role of the PERG and to examine whether there may be specific PERG changes in particular disease processes. Preliminary accounts of these findings have been presented.[18 19]

Materials and methods

The checkerboard PERG was recorded by our standard techniques.[20] Gold foil recording electrodes (Carter and Hogg, London) were placed in the fornix of the lower eyelid and referred to ipsilateral outer canthus silver-silver chloride electrodes with a mid forehead earth. Ipsilateral temple electrodes have been shown to minimise any possible contamination from the PVEP.[21] The signals were processed by a Nicolet CA1000 averaging computer with internal artefact rejection and a bandwidth of 1–100 Hz–3 dB. There were a minimum of 200 averages per trial with a minimum of two trials performed to confirm the reproducibility of the waveform. Checkerboard pattern reversal stimulation was performed by a Digitimer moving mirror stimulator subtending a total field of 14° at the eye with an individual check size of 34′. Mean luminance was 400 cd/m² with 89% contrast. Stimulation rate was 4·8 reversals/s, with an analysis time of 200 ms. (In some earlier recordings a rate of 6 reversals/s with an analysis time of 100 ms was used.) Binocular stimulation was performed, spectacle correction being used where appropriate. The advantage of binocular registration of the PERG is that, in patients with a unilateral reduction in visual acuity, fixation is maintained by the eye in which acuity is preserved.

Correspondence to Dr G E Holder.

It is our experience that blink artefact can be a major problem in obtaining consistent recordings even when using the integral artefact reject system of the averager. We therefore use a technique of 'interrupted stimulation' which we find effective in minimising this type of artefact. The patient is instructed to look at the central fixation spot and to try not to blink while the pattern is moving. Every 4–6 s stimulation is interrupted, the patient told to blink a few times, and stimulation then resumed. We find this technique to be much more effective in obtaining waveforms of low variability than purely relying on the artefact reject system of the averager.

The patients described form part of a larger population routinely referred for electrodiagnostic assessment, mostly by neurologists, neurosurgeons, or ophthalmologists and have been selected for this study only because they had abnormal PERGs.

The normal control group consisted of volunteer members of the hospital staff with no significant ophthalmic or neurological history other than possible corrected refractive error.

Results

The normal checkerboard PERG recorded under our standard conditions consists of a prominent positive component at 52 ms (P50) followed by a larger negative component at some 93 ms (N95). In some patients a small early negative component at some 35 ms is also present. There is a superficial similarity between this waveform and the flash ERG which has led some authors to use the term 'b-wave' to describe the main positive component of the PERG.[11–22] We have not adopted this terminology because it is unlikely that these components represent the same physiological processes. We merely describe the components by their polarity and approximate mean latency. If it is thought that this may lead to confusion with components of the pattern visual evoked potential (PVEP), perhaps the terms α, β, and γ could be used to avoid confusion with flash ERG components.[23] The 'p', 'q', and 'r' terminology of Kirkham and Coupland[24] is not thought to be appropriate, as these terms have long established uses in electrocardiography.

Analysis of the PERG concentrated on the latency of P50, and the peak P50 and N95 amplitudes as measured from their points of onset. The intraocular N95:P50 ratio and the interocular ratios were also calculated.

Table 1 *PERG normal values (16 subjects, 18–48 years, mean age 27·4 years)*

Latency (ms)	*Range*	*Mean*	*SD*
P50	48–55	51·67	2·25
N95	87–100	93·11	3·48
Amplitude (μV)			
P50	2·5–5·0	3·74	0·81
N95	3·6–8·0	5·71	1·15
N95:P50	1·25–2·0	1·54	0·18
Interocular ratios			
P50	0·88–0·97	0·93	0·04
N95	0·83–0·98	0·92	0·05
N95:P50	0·85–0·96	0·93	0·03

Normal values are shown in Table 1. Of particular interest is the relatively high degree of interocular symmetry (shown by the low variability of the interocular ratios). This confirms the results of Arden *et al.*[25] but is in disagreement with the high variability found by Kirkham and Coupland.[26] Although we consider that the relatively low variability of our findings is at least in part due to our recording technique using 'interrupted stimulation' (see above), we do not have an explanation for this apparent discrepancy between the findings of other authors. An important feature of our waveform analysis is the use of the intraocular N95:P50 amplitude ratio. This stable measure can be particularly useful in the assessment of patients with bilateral disease (see Fig. 3).

The results in patients are shown in Table 2. The criteria for abnormality were set at 2·5 standard deviations from mean values. In most cases the PERG changes were restricted to amplitude. In two patients, however, one with a central retinal vein occlusion, and one with a retinal detachment, the P50 latency was increased. It is of particular interest that two patients with optic nerve disease showed an abnormality confined to the N95 component when first examined but had developed a P50 abnormality at follow-up.

Table 2 *Pattern ERG findings in 72 patients with anterior visual pathway dysfunction*

	No. of patients	*PERG abnormality*	
		P50±N95	*N95 only*
Retinal disease, e.g., retinitis pigmentosa, retinal vascular lesions, maculopathy, cone dystrophy, etc.	28	28	0
Reduced acuity due to cataract	2	2	0
Optic nerve disease, e.g., demyelination, compression, ischaemic optic neuropathy, etc.	36*	9*	29*
Glaucoma	3	3	0
Amblyopia	2	2	0
Congenital optic disc abnormality	1	0	1

*Two patients with optic nerve demyelination initially showed an amplitude reduction confined to N95, but subsequent follow-up examination revealed the development of a P50 abnormality.

Illustrative examples of the findings in patients with retinal and optic nerve disease are shown in Figs. 1–3. All PERGs are the superimposition of two trials to demonstrate the reproducibility of the waveform. The patient with the maculopathy was selected because the PERG from the affected eye is present but reduced. In the patients with severe pigmentary retinopathy and central retinal involvement, in cone dystrophies, senile disciform macular degeneration, etc., the PERG was usually absent from affected eyes. In no case of optic nerve disease, including one eye with 'no perception of light' due to optic nerve compression from a pituitary tumour, was the PERG completely absent.

Discussion

The PERG abnormalities of the patients in our study with generalised retinal or macular dysfunction occur in the main positive (P50) component. This is in agreement with the findings of previous authors.[9,24,27] Other reports of PERG abnormalities in macular disease have also appeared,[7,28] but the authors used steady state stimulation, which precludes individual

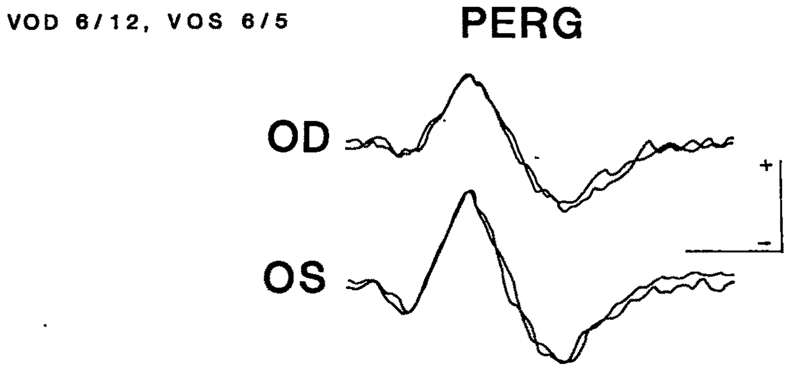

Fig. 1 *Pattern ERG findings in a patient aged 20 with a right maculopathy. The P50 component is of significantly reduced amplitude in the recordings from the right eye. Calibration 3 μV, 40 ms.*

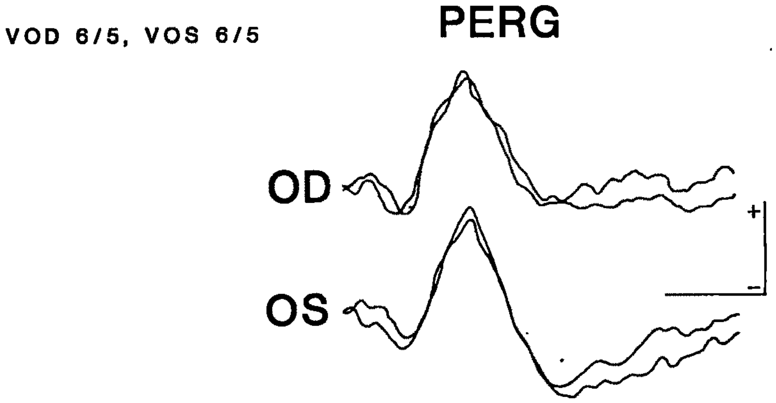

Fig. 2 *Pattern ERG findings in a patient aged 39 with multiple sclerosis and right retrobulbar neuritis. The N95 component is of significantly reduced amplitude in the recordings from the right eye, the P50 component being unaffected. Calibration 3 μV, 40 ms.*

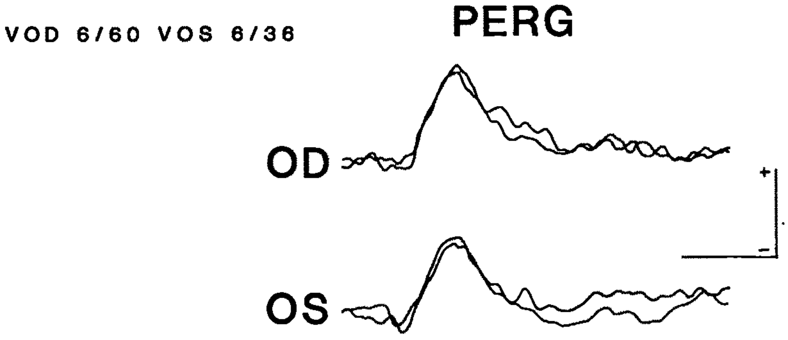

Fig. 3 *Pattern ERG findings in a patient aged 64 with bilateral idiopathic optic atrophy. The N95 component, as reflected in the N95:P50 intraocular ratio, is bilaterally subnormal. Calibration 3 μV, 40 ms.*

P50 and N95 assessment. It is similarly difficult to compare the present findings in optic nerve disease with previous reports from authors using steady state stimulation.[7 8 15] Other authors [6 10 13 16] have examined the P50 component of the transient PERG and described abnormalities of this component associated with optic nerve dysfunction. Although abnormalities of the P50 component occurred in some of our patients, the predominant abnormality (81%) we observed in patients with abnormal PERGs and optic nerve disease was involvement of the N95 component, the P50 component being spared. In addition, although absent PERGs were often seen in patients with retinal dysfunction, no patient with optic nerve disease had an absent PERG.

Indeed, the most important feature of our results is the selective effect of different pathological conditions on the two PERG components studied. In no patient in our series with retinal or macular disease was an abnormality confined to the N95 component; the P50 component was involved in all patients with abnormal PERGs and retinal dysfunction. In contrast, 81% of our patients with optic neuropathies and abnormal PERGs showed an abnormality confined to the N95 component. Porciatti and von Berger[11] have previously noted that in some patients with optic nerve disease the N95 component may be affected, but unfortunately they supplied no further details. We have been unable to trace any other clinical report including analysis of this component. Our findings establish that the N95 component is the more sensitive indicator of optic nerve dysfunction and also suggest that failure to examine this component may result in false negative examinations. This may explain some of the discrepancies between previous authors as to the incidence of PERG abnormalities in optic neuropathies: abnormalities of the P50 component to which other authors have restricted their attention occurred in only 19% of our patients with optic nerve dysfunction and abnormal PERGs. Our findings also appear to refute the conclusions of Kirkham and Coupland[16] and Ota and Miyake[17] that the PERG has little value in the assessment of optic nerve disease.

The results also readily lead to speculation as to the site or sites of origin of the PERG. Berninger and Schuurmans[21] have reported that the late negative component of the checkerboard PERG (our N95) exhibits spatial tuning in normal subjects, concluding that the retinal ganglion cell layer is therefore involved in its generation. Similar conclusions have also been drawn for the second harmonic component of the steady state PERG.[14] Our results in patients with optic nerve disease and abnormal PERGs provide clinical evidence to support the theory that the N95 component of the PERG is generated in the proximal retina, presumably the ganglion cells, which would be expected, at least in the fullness of time, to show abnormalities due to retrograde degeneration.

It is important here, particularly if the PERG is to play a significant part in the diagnostic armamentarium, to ensure that the PERG, particularly the N95 component, is independent of the cortically generated visual evoked potential (VEP). Berninger and Schuurmans[21] extensively investigated the effects of different reference electrodes and concluded that, if an ipsilateral temple reference (similar to that used in our study) is used, there is no doubt that both the P50 and the N95 components are generated in the retina and do not reflect contamination from the VEP. Plant *et al.*[15] reached similar conclusions for the steady state PERG. Our own observations in patients lead to similar conclusions when pattern VEP data are considered (in preparation). Examples illustrating this dissociation between the PERG and the pattern VEP are shown in Fig. 4.

It is more difficult to draw conclusions as to the site of origin of the P50 component from our data. This component was affected in all our patients with macular or generalised retinal dysfunction, which would be expected to primarily involve distal retinal layers in patients with glaucoma and in patients with reduced visual acuity due to cataract. The selective involvement of the P50 and N95 components in different pathological states does, however, suggest that they are generated in different retinal layers, in keeping with the suggestion of Berninger and Schuurmans.[21] These authors[30] have also suggested, using low stimulus luminous levels, that the main positive component of the PERG is luminance related, whereas the late negative component is contrast related. This observation resulted in the conclusion that the late negative component is probably generated in the ganglion cells, the main positive component being generated more distally.

In conclusion, the N95 component of the PERG is selectively affected in 81% of the patients studied with definite optic nerve disease and abnormal PERGs, invovement of the P50 component only occurring in 19% of the cases examined. The P50 component, however, was invariably affected in retinal disease, in glaucoma and in reduced visual acuity due to cataract, no such patient having a PERG abnormality confined to the N95 component. In addition, delayed PERGs were seen only in retinal dysfunction, and in one of those patients a pattern VEP delay of similar magnitude was observed. It has previously been reported[31] that retinal dysfunction can give rise to delayed pattern VEPs, even in the presence of normal visual acuity, and it is now standard practice in our clinic to record the PERGs in

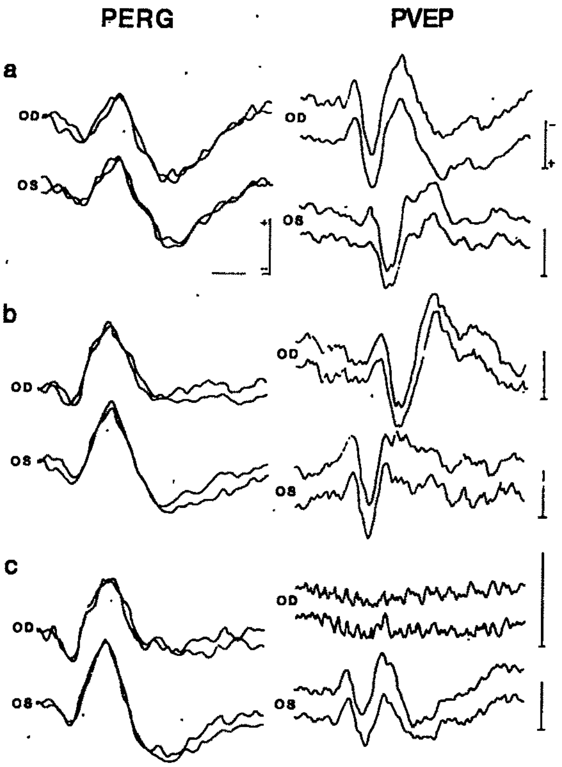

Fig. 4 *Pattern VEP and pattern ERG (PERG) findings in three patients with optic nerve demylination which demonstrate the independence of the N95 component of the PERG and the pattern VEP.* (a) *A patient with a unilateral pattern VEP delay but normal, symmetrical PERGs.* (b) *A patient with a unilateral pattern VEP delay with a unilateral N95 amplitude reduction in the PERG from the affected eye.* (c) *A patient with a unilateral pattern VEP extinction and a unilateral N95 amplitude component reduction in the PERG. PERG traces are the superimposition of two trials to demonstrate the reliability of the waveform. Pattern VEPs are recorded from the right (upper trace) and left hemispheres in response to monocular stimulation of each eye in accordance with our standard techniques.*[23] *Calibration for all PERGs 3 µV, 40 ms. VEP analysis time 320 ms, amplitude calibration 5µV.*

any patient with a delayed VEP. Certainly the diagnostic indicators detailed in the present report confirm the role of the PERG in the assessment of patients with anterior visual dysfunction, and it is therefore suggested that PERG recording should be a routine part of an ophthalmic electrodiagnostic protocol, particularly if there is a suspicion of optic nerve disease.

I am indebted to Dr Gordon Plant for access to material in press, to Mr John Shilling for his comments on the original version of this manuscript, and to the Medical Photography Department, Greenwich District Hospital, for assistance with the figures.

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Intracranial extension of choroidal melanoma via the optic nerve*

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SUMMARY A 62-year-old woman was treated with cyclocryotherapy for neovascular glaucoma of uncertain origin. Fifteen months later she was diagnosed as having a choroidal melanoma, which extended extrasclerally to fill the orbit and invaded the optic nerve intracranially to the chiasm. She was treated by orbital exenteration and neurosurgical resection of the intracranial portion of the optic nerve. The patient is alive and clinically free of metastasis five years after the onset of neovascular glaucoma and almost four years after surgical resection. The significance of this highly unusual growth pattern of uveal melanoma is discussed.

Invasion of the optic nerve by uveal melanoma is rare.[1] In a histopathological review of 2535 cases of uveal melanoma Wilder and Paul[2] reported that only 0·6% of choroidal and ciliary body melanomas invade the optic nerve. Microscopically the majority of juxtapapillary uveal melanomas stop abruptly at the optic disc margin and do not extend into the axial portion of the optic nerve. We report a case of choroidal melanoma with massive orbital invasion and extensive optic nerve infiltration to the optic chiasm.

Case report

A 62-year old white woman with no prior medical or ocular problems noted soreness of her left upper eyelid in December 1980. She was diagnosed as having neovascular glaucoma and a dense cataract in the left eye. Ophthalmoscopy of the involved eye was limited because of the lens opacity. The patient was treated with topical corticosteroids, atropine, and two courses of cyclocryotherapy, but her intraocular pressure remained elevated. B scan ultrasonography of the left eye revealed a retinal detachment with either tumour or subretinal blood. The patient declined further examination and was followed up at periodic intervals for glaucoma and pain control.

She noted a gradual onset of a 'bulging' left eye in March 1982 and was found to have proptosis, limited extraocular motility of the left eye, and an orbital mass. She was referred to the Wills Eye Hospital Ocular Oncology Service for further treatment.

Ocular examination revealed a visual acuity of 6/6 (20/20) in the right eye and no light perception in the left eye with a Marcus Gunn pupil. Examination of the right eye revealed no abnormal findings. Hertel exophthalmometry demonstrated 14 mm of left proptosis. Ductions of the left eye were severely limited in all fields of gaze, and external examination revealed a 4×3×3 mm firm subcutaneous mass inferior to and including the left lower eyelid (Fig. 1). Biomicroscopy of the left eye showed early band keratopathy, shallow anterior chamber, diffuse iris atrophy, and a dense cataract displacing the iris anteriorly (Fig. 2). Intraocular pressures were 16 mmHg in the right eye and 64 mmHg in the left eye, and gonioscopy of the left eye revealed a completely closed angle. The dense cataract precluded an ophthalmoscopic view of the fundus.

B scan ultrasonography and computed tomography (CT) of the orbits showed a large mass filling the globe and entire orbit (Fig. 3). A Goldmann visual field of the right eye did not reveal any defects suggesting chiasmal or right optic nerve involvement.

A fine needle aspiration biopsy of the inferior

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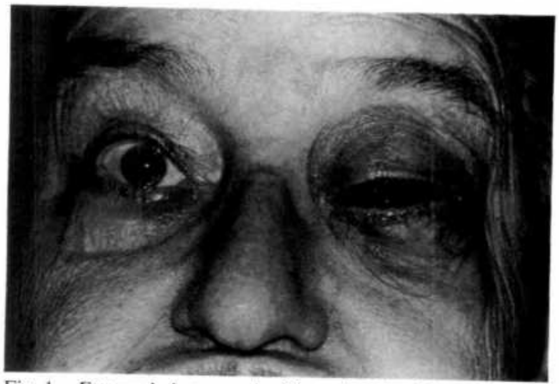

Fig. 1 *External photograph of face showing left proptosis, periorbital oedema, and conjunctival injection.*

orbital mass revealed malignant cells (class V) compatible with malignant melanoma (Fig. 4). A thorough systemic examination with liver enzymes, chest *x*-ray, and liver CT showed no evidence of distant metastases.

The patient's left orbit was exenterated with a lid sparing technique. At the time of surgery the transected optic nerve near the orbital apex was found to be black. Further resection of the optic nerve to the posterior portion of the optic canal continued to show black infiltration of neural tissue into the optic foramen. Because of the extension of the tumour into the optic canal the patient was referred for neurosurgical evaluation. It was decided to resect the prechiasmal portion of the left optic nerve. Postoperatively the chiasm was irradiated with a total fractionated dose of 6000 rad. (60 Gy).

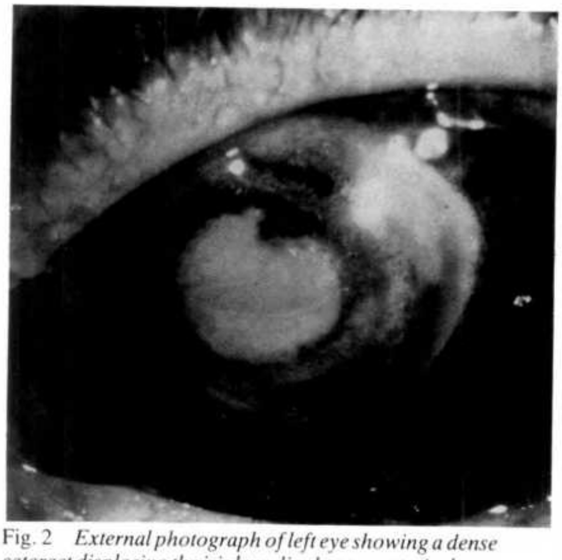

Fig. 2 *External photograph of left eye showing a dense cataract displacing the iris lens diaphragm anteriorly.*

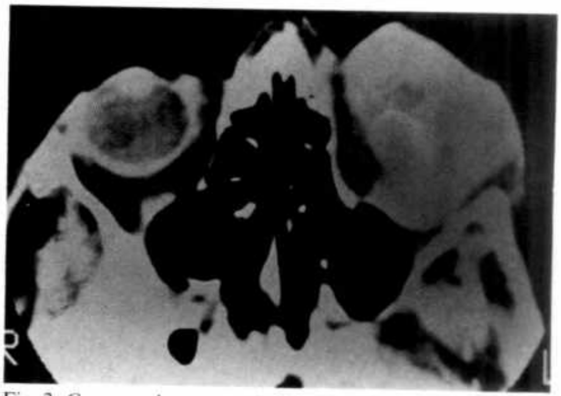

Fig. 3 *Computed tomography of the orbits showing the left eye filled with a dense mass with extensive orbital involvement.*

The patient had no further problems until December 1984, when she developed an enlarged preauricular node, which was excised and found to contain malignant melanoma cells. A further search for metastases was negative, and the patient was treated with local radiotherapy to the left preauricular and cervical lymph nodes.

The patient is alive, well, and free of distant metastases five years after her initial presentation.

PATHOLOGY

The exenteration specimen consisted of the eyelids, globe, and periocular orbital tissue. Gross examination of the sectioned specimen showed a globe filled with a light brownish grey mass pushing the opaque lens forward and flattening the anterior chamber. A multilobulated, firm, tan coloured mass (23×36 mm) emerged from the inferotemporal aspect of the globe to replace completely the periocular tissue. The optic nerve was black along its entire length, without gross evidence of dural pigmentation (Fig. 5).

Microscopic examination showed a massive tumour filling the vitreous cavity and displacing the iris-lens diaphragm anteriorly. The atrophic iris was flattened against the corneal endothelium. The lens showed dense nuclear sclerosis and liquefaction of the cortex with a ruptured capsule. The ciliary body was atrophic.

The tumour was composed predominantly of epithelioid melanoma cells (Fig. 6) with nuclear pleomorphism and numerous mitotic figures. Focal areas of tumour necrosis were present. On cross-section of the optic nerve, there was profound optic atrophy and focal aggregates of erythrocytes with melanocytic neoplastic cells infiltrating the pial columns to the site of transection. The subarachnoid space and dura mater were free of tumour cells.

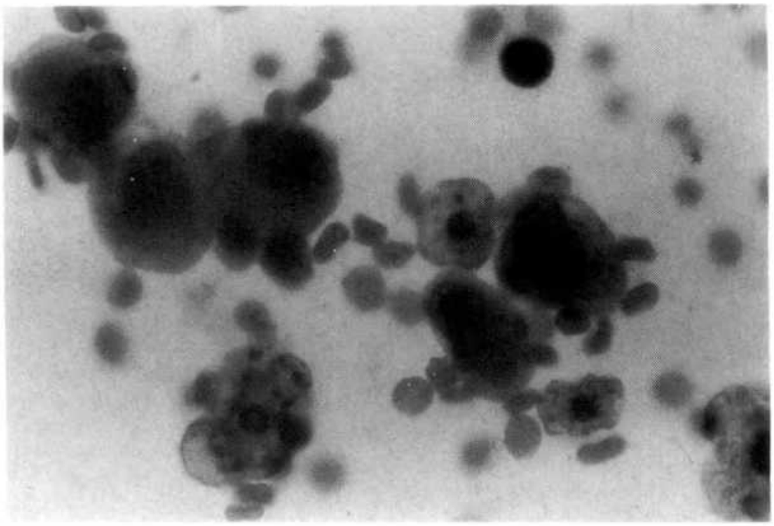

Fig. 4 *Cytology of the fine needle aspiration biopsy showing large rounded malignant melanoma cells with characteristic cytoplasmic pigment granules. Papanicolaou stain.*

Discussion

Optic nerve extension of uveal melanomas is rare. Optic nerve extension of choroidal or ciliary melanomas occurred in 3·7% of 432 cases reviewed by Shammas and Blodi[3] and 0·6% of 2535 cases reviewed by Wilder and Paul.[2] Most juxtapapillary choroidal melanomas stop abruptly at the disc margin and do not invade the optic nerve. However, in the rare case of neural invasion several predisposing risk factors have been identified. These risk factors included elevated intraocular pressure, large tumour size, diffuse growth pattern, peripapillary location, epithelioid cell type, and tumour necrosis.[3-6]

Spencer[5] reviewed 10 cases of uveal melanoma (eight choroidal and two iridociliary) that histopathologically showed optic nerve extension. All the eyes had no perception of light, angle closure glaucoma, and cavernous degeneration of the optic nerve. He proposed that the mechanism of optic nerve invasion involved tumour seeding into the vitreous with subsequent invasion of the optic nerve. The cavernous spaces of glaucomatous optic atrophy have been shown to contain hyaluronic acid, presumably of vitreous origin. It is possible that the vitreous substance within the cavernous spaces carried the neoplastic cells into the nerve.

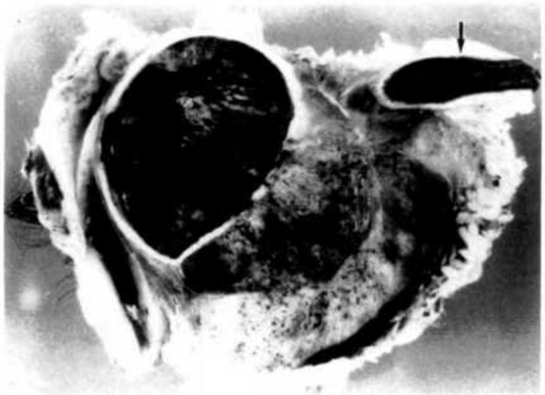

Fig. 5 *Gross examination of the exenteration specimen showing the globe, orbit, and optic nerve with tumour infiltration. Note the black colour of the optic nerve (arrow).*

Spencer[5] emphasised that absence of light perception is distinctly unusual in typical cases of uveal melanoma, but it was characteristically found in his series of melanomas with optic nerve extension. Shammas and Blodi[3] reported 16 cases of peripapillary choroidal melanomas that extended into the optic nerve and 10 cases of peripapillary melanomas that were without optic nerve extension. They found that all the eyes with optic nerve extension were blind and glaucomatous and only one eye without optic nerve extension was blind or glaucomatous. Thus absence of light perception in an eye with a melanoma may suggest the presence of optic nerve invasion by the tumour.

Large tumour size[6] and diffuse growth pattern[7] are also factors associated with optic nerve extension. Diffuse growth pattern of choroidal melanoma is defined as tumour mass involving a minimum of one-quarter of the uvea (including the iris and ciliary body) and less than 7 mm in height.[8] This represents only 5% of all choroidal melanomas, and this tumour type is frequently misdiagnosed because of its flat appearance.[8] Brown and Shields[7] reported two cases of diffuse choroidal melanoma with optic disc oedema. On histopathological examination of the

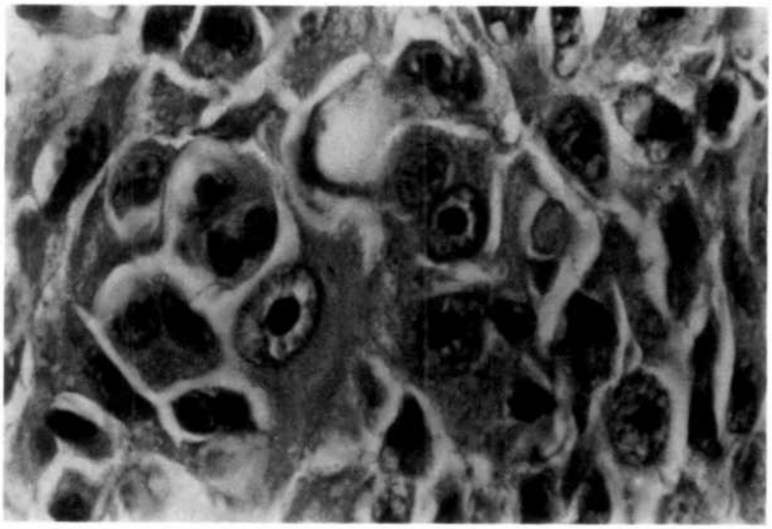

Fig. 6 *Photomicrograph showing epithelioid melanoma cells. Haematoxylin-eosin.*

two cases only one had optic nerve invasion. They pointed out that optic nerve invasion was characterised by a swollen yellow optic disc which was hypofluorescent on fluorescein angiography. Preoperative determination of possible optic nerve extension is important in assessing the prognosis for the patient and in planning surgery with attempts to obtain a long section of nerve at enucleation.[4,5]

Uveal melanomas are termed peripapillary when they surround the optic nerve head. In 1973 Scuderi[9] reported a case of peripapillary melanoma with optic nerve extension. Shammas and Blodi[3] reported 26 cases of peripapillary melanoma and claimed 61·5% extended into the optic nerve and 46·2% extended into the subarachnoid space. Our experience at Wills Eye Hospital Oncology Service has been that nodular peripapillary melanomas have little tendency to invade the nerve, while diffuse, relatively flat peripapillary melanomas show a marked propensity for optic nerve extension.

The type of cell was epithelioid or mixed in all 10 cases of optic nerve extension of uveal melanoma reported by Spencer[5] and in 87·5% of the cases of optic nerve extension reviewed by Shammas and Blodi.[3] Likewise the cases reported by Chess and associates[6] and Scuderi,[9] and the case we report here, were tumours composed of epithelioid cells. Within the epithelioid cell mass tumour necrosis has commonly been described.[2,3,5]

Management of choroidal melanomas with optic nerve extension requires a gentle enucleation with excision of a long piece of optic nerve.[3,5] Observation of the cut surface of the optic nerve during the surgical procedure may reveal incomplete excision of tumour by a typical black colour of the transected edge. This finding should direct the surgeon to excise a more posterior portion of the nerve.[5] It is uncertain whether complete local excision improves the systemic prognosis. Spencer[5] believes that the poor prognosis is related to the features associated with optic nerve invasion such as epithelioid cell type, necrosis, and large tumour size. Shammas and Blodi[3] state that the prognosis of choroidal melanoma with optic nerve extension is dependent primarily on the presence of concurrent orbital invasion.

The role of exenteration and/or radiotherapy for uveal melanoma with extrascleral extension is uncertain[1,3,10-13] Our patient, with massive extraocular spread, was treated with orbital exenteration, neurosurgical resection of the intracranial portion of the optic nerve, and postoperative radiotherapy. Although optic nerve extension is considered a poor prognostic sign,[14] our patient is healthy and without evidence of distant metastases at the time of this writing, five years after she presented with a blind painful eye.

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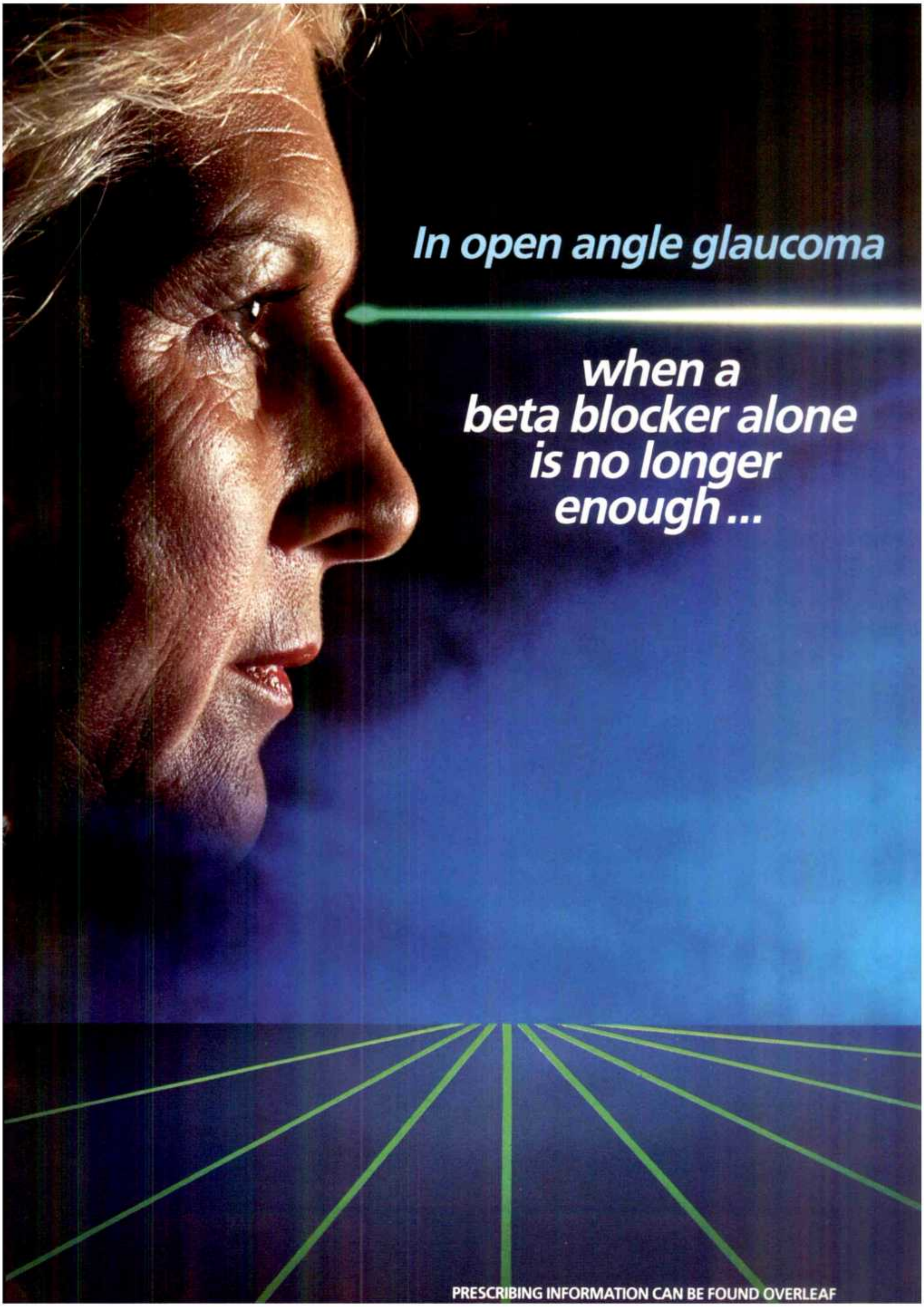
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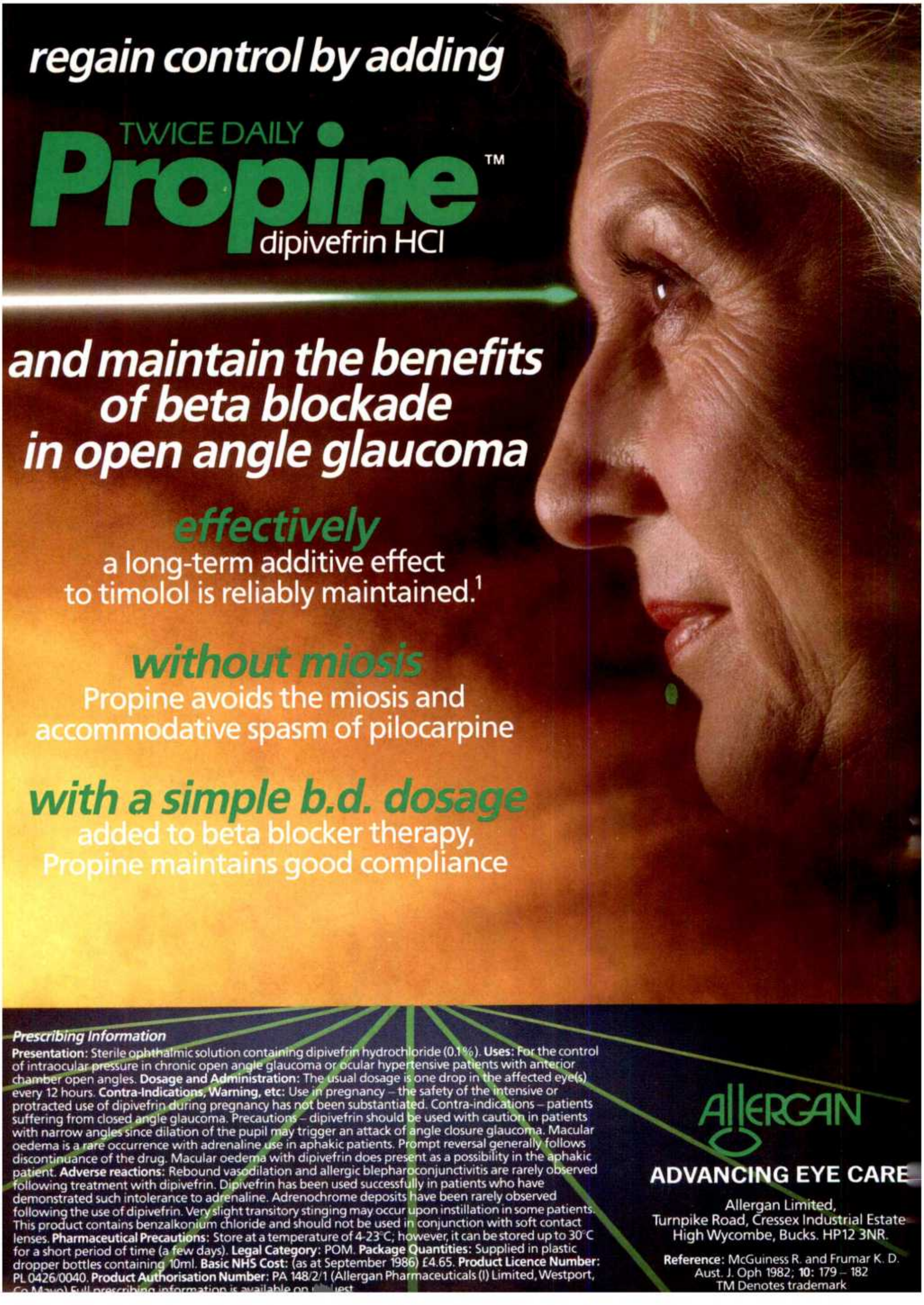

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Intraocular pressure during cardiopulmonary bypass

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SUMMARY Intraocular pressure was measured in 24 patients undergoing elective cardiopulmonary bypass surgery. There was a rapid rise when the bypass circulation began, and this was maintained for about 30 minutes. A simultaneous drop in arterial perfusion pressure and packed cell volume occurred. We suggest that marked haemodilution is responsible for this effect, through increased ocular blood flow and low colloidal osmotic pressure. The possible aetiological significance in relation to ischaemic optic neuropathy complicating cardiopulmonary bypass is discussed.

In this study intraocular pressure (IOP) was recorded with a pneumatonometer at specific times before, during, and after cardiopulmonary bypass (CPB) and the values were correlated with other variables. Despite a lowering of arterial pressure, IOP did not decrease but was increased in all cases.

Two previous studies of IOP during bypass surgery have been performed and conflicting results reported. Stellpflug *et al.*[1] reported 6–7 mmHg rise in IOP with arterial pressure maintained at 60 mmHg. Lilleaasen and Hørven[2] found that the IOP did not vary significantly from pre-CPB values.

Materials and methods

Twenty-four patients were studied, of average age 55 (range 29–59) years. All were undergoing elective coronary artery bypass graft or valve replacement surgery. None had known eye disease. Informed consent for measurement was obtained from each patient.

Anaesthesia was induced with thiopentone and midazolam. Pancuronium was used for muscle relaxation; anaesthesia was maintained with 50% nitrous oxide-oxygen mixture and intrathecal morphine given. Extracorporeal circulation was maintained with a Stockert non-pulsatile pump and Cobe CML membrane oxygenator. The pump was primed with 2 litres of Hartmann's solution, 25 g mannitol, 60 mEq (mmol) sodium bicarbonate, and 100 mg heparin. This solution is slightly hypertonic (357 mosmol/kg water).

The IOP was measured with a Digilab pneumatonometer, which is an easy, non-invasive method and gives a permanent record. Calibration was monitored before each case with a Digilab verifier and accuracy checked with Goldmann applanation tonometry at intervals.

Arterial and central venous pressures were monitored via catheters in the radial artery and subclavian vein. Transducers were used for measurement and were calibrated against a mercury column. Blood gas, acid base and haematocrit (packed cell volume) determinations were performed on an ABL-2 instrument (Radiometer, Copenhagen).

Measurements were performed at scheduled times as follows. The IOP was measured in the right and left eyes on several occasions prior to CPB, 5, 10, 15, 25, 45 minutes after the beginning of CPB, and on further occasions after cessation of CPB. Mean values for right and left IOP readings were calculated, and then mean values for the periods before and after CPB were used for analysis.

Blood gas, acid base status, and packed cell volume were measured at the same time as the IOP. Carbon dioxide and oxygen were maintained at normal temperature corrected values throughout the procedure. Body temperature was maintained between 27 and 29°C during CPB.

Continuous values of arterial and central venous pressures were available. Non-pulsatile arterial perfusion pressure was maintained between 45 and 70 mmHg during CPB except at short intervals of deliberate hypotension in 9 patients (see below). The mean central venous pressure before CPB was approximately 7 mmHg. It was not allowed to exceed

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this level during bypass, and a variable decrease to below zero was noted in most patients.

Statistical evaluation was by the *t* test applied to a paired comparison.

Results

At the beginning of CPB a significant ($p<0{\cdot}001$) fall in packed cell volume was observed. This occurred within 5 minutes of infusion of bypass pump priming fluid. It remained stable during CPB, and increased gradually after CPB. The blood pressure was also significantly reduced during CPB ($p<0{\cdot}001$) (Table 1).

The IOP rose immediately in 21 patients, and had risen within 10 minutes of CPB in all patients. The mean elevation for all patients was significant ($p<0{\cdot}001$). Gradual return to pre-CPB level was noted at 25 and 45 minutes. A less significant rise was seen at cessation of CPB ($p<0{\cdot}02$) (Table 2 and Fig. 1).

The central venous pressure fell to varying levels. No significant disturbances in pH or blood gases occurred.

The increase in IOP correlated with observed haemodilution. A ratio of haemodilution (packed cell volume before/during CPB) and ratio of IOP (highest IOP during/mean IOP before CPB) was calculated for each patient and a graph plotted (Fig. 2). A regression line was plotted from the formula $y=a+bx$, where y=expected value of y for any value of x, and b=line slope.[3] The correlation coefficient $r=0{\cdot}46$.

No complications were associated with measurement procedures.

Table 1 *Arterial pressure and packed cell volume during surgery*

	Arterial pressure (mmHg), mean±standard error	*Packed cell volume (%), mean±standard error*
Pre-CPB	102·1±2·4	39·0±0·9
During CPB	59·9±1·6	23·7±0·75
Post-CPB	92·1±3·2	

Table 2 *Mean IOP of all patients during surgery*

Time	*Mean IOP (mmHg)*	*Standard error*
Pre-CPB	16·5	0·53
On CPB 5 min	20·8	0·75
On CPB 10 min	20·9	0·77
On CPB 15 min	21·1	0·84
On CPB 25 min	19·95	0·98
On CPB 45 min	17·1	0·69
Post-CPB 5–10 min	19·25	0·83

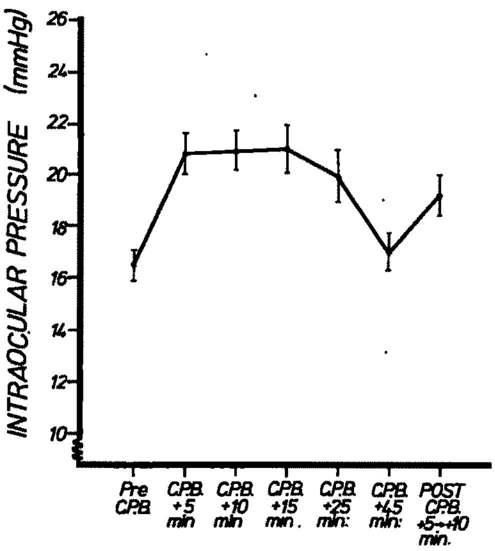

Fig. 1 *IOP of all patients (mean and SEM) calculated from mean of each at specified times. As CPB is discontinued in a phased manner, it was not possible to state the precise time post-CPB at which readings were taken.*

Discussion

IOP regulation during CPB is multifactorial, and no clear explanation is evident for the rise observed.

Several factors during CPB reduce aqueous production, particularly hypothermia,[4] hyperosmolarity[5]

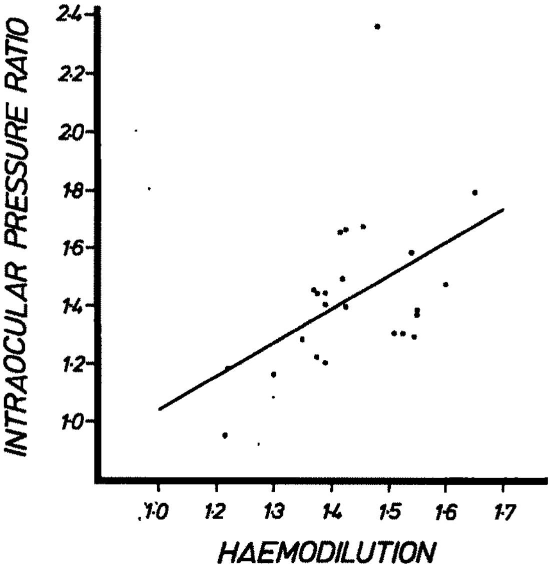

Fig. 2 *Haemodilution ratio for each patient calculated from packed cell volume before/during CPB. IOP ratio calculated from highest value during/mean before CPB.*

of the infused pump priming fluid, and reduced arterial pressure. Aqueous production is unaffected by reduction of perfusion pressure to 70–90 mmHg, but when reduced to 40–60 mmHg production falls sharply.[6] Presumably this is due to reduced blood flow through the ciliary processes. In nine patients whom we studied perfusion pressure was reduced to 10–15 mmHg for short periods to facilitate surgery, and we noted that the IOP fell immediately to levels around 5 mmHg. Recovery to maintenance levels was immediate also. 25 g mannitol was a component of the pump priming fluid in all patients, and this is probably the cause of IOP reduction within 30 minutes of infusion. Constricted pupils were noted for a period of up to 24 hours after surgery; this is probably an effect of the dose of intrathecal morphine given at the beginning of anaesthesia and would tend to lower the IOP.

Reduced protein content of the blood plasma and low colloidal osmotic pressure increased aqueous production.[7] Haemodilution by the pump priming fluid has this effect, and this partly explains a correlation with rise in IOP. However, the rapid rise in IOP observed would not be fully explained by this non-mechanical cause.

Immediately increased blood flow to the ciliary processes on infusion of pump priming fluid would be a more probable cause. Middle cerebral and internal carotid artery flow velocity has been shown to increase to as much as 300% of pre-CPB levels, and this increase is related to degree of haemodilution.[8] The proportion of aqueous produced by active transport is uncertain, estimates ranging from 35% to 80%.[9] This energy consuming function of the ciliary epithelium requires high oxygen delivery either through increased blood flow, increased blood oxygen content, or decreased affinity of haemoglobin for oxygen. Flow velocity is therefore a critical determinant of the total amount of oxygen released if oxygen content is maintained. Increased flow velocity may compensate for rapid reduction in arterial pressure.

Hormonal changes in CPB may possibly contribute to maintenance of elevated IOP, but would not be responsible for the immediate rise seen. Little systematic experimentation into hormonal effects on the IOP has been performed.

Our findings are similar to those in 50 patients of Stellpflug *et al.*,[1] who showed that a decrease in arterial pressure to 57 mmHg during CPB caused an increase of 6–7 mmHg in IOP. They measured the IOP only 5 and 10 minutes after the start of CPB, and did not specify how the pump was primed. Lilleaasen and Hørven[2] primed the pump with a solution of high osmolality. It is of interest that similar work on pigs showed an increase in IOP during the haemodilution phase and a parallel increase in intracranial pressure.[10] This shows that tissue fluid content changes are not limited to the eye and raises the possibility of changes in the choroid plexus analogous to those in the ciliary processes. In preference to a Schiøtz tonometer, which was used in the above studies, we used a pneumatonometer. A permanent record was thus obtained and observer error minimised.

Clinical implications of elevated IOP during CPB are not clear. Some elevation or even maintenance of IOP in a setting of arterial pressure reduced to 40–70 mmHg may be especially relevant to posterior ciliary artery supply to the optic disc head. Anterior ischaemic optic neuropathy (AION) involves infarction of the optic nerve head due to compromise of the arterial supply to the laminar and prelaminar regions. Nine cases following CPB have been reported,[11 12] bilateral AION occurring in three; in addition two cases of bilateral AION have occurred in our departments. Sustained elevation of IOP together with reduced ciliary artery perfusion pressure, and a substantial rise in levels of the potent vasoconstrictor angiotensin,[13] are likely causes of AION complicating bypass.

Further study of the behaviour of the IOP during bypass will be of benefit, particularly the influence of pulsatile perfusion, manipulation of priming fluid osmolality, and of mannitol administration 30 minutes prior to haemodilution with pump priming fluid.

We thank Dr Leslie Daly for his assistance with statistical analysis.

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Pressure compliance of the optic nerve head in low tension glaucoma*

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SUMMARY Twenty eyes of 10 healthy subjects, 11 eyes of seven patients with low tension glaucoma, and three eyes of three patients with ischaemic optic neuropathy were investigated. Visual evoked responses were recorded under stepwise artificially increased intraocular pressures. The results of the visual evoked response recording (pressure compliance test) allow a clear distinction to be made between healthy subjects, patients with low tension glaucoma, and patients with ischaemic optic neuropathy. In the groups investigated a lack of autoregulation of the optic nerve head circulation was found in patients with low tension glaucoma only. Patients with anterior ischaemic optic neuropathy showed the same pressure compliance behaviour as healthy subjects. The methods used here seem to provide a practicable clinical tool in the differential diagnosis of low tension glaucoma.

Discussion on the aetiology of low tension glaucoma started in 1862, when von Graefe[1] for the first time observed a glaucomatous atrophy of the optic nerve head without a rise in intraocular pressure. Since then a variety of pathogenetic concepts have been discussed. Opinions are still controversial, especially with regard to the vascular origin of low tension glaucoma.

Walker *et al.*[2] examined the hypothesis that generalised ischaemic vascular diseases may lead to an aspect of low tension glaucoma via a reduced blood supply. However, he did not find the interrelations to be statistically significant. The question has also been considered whether stenosis of the vessels supplying the brain might be causally connected with the eye disease.[3,4] In 1952 Etzikson[3] suggested a pathogenetic relation between radiologically detectable stenosis of the internal carotid artery and low tension glaucoma. Drance *et al.*[4,5] shared this opinion as regards unilateral stenosis of the carotid artery with equilateral low tension glaucoma, but Chandler and Grant[6] did not observe any connection between the two conditions. In 1973 Drance *et al.*[5] determined the blood pressure in the ophthalmic artery by means of impression ophthalmodynamometry. They thus discovered a reduction of the perfusion (in relation to the blood pressure of the upper arm) in patients with low tension glaucoma by comparison with those having primary open angle glaucoma (POAG) and normal persons. Hager[7] obtained similar results by means of ophthalmodynamography.

Before diagnosing low tension glaucoma, various possible factors should be excluded. Intracranial diseases (tumours, etc.) and ischaemic diseases of the optic nerve might imitate glaucomatous atrophy of the optic nerve and scotomas. As generally accepted, rigidity reductions of the sclera in myopia cause intraocular pressures which appear too low if they are measured by impression tonometry; the condition may therefore imitate low tension glaucoma. The problems described and the fact that it is often difficult to diagnose low tension glaucoma lead to the question whether it is possible to obtain indications of the existence and aetiology of low tension glaucoma by a clinically practicable non-invasive method. In recent years several authors[8,9] have tried to describe the pressure compliance of the optic nerve head in healthy subjects and in various types of glaucoma. Ulrich and Ulrich[9] showed, in a single case, by electroencephalodynamography that a lowered pressure compliance of the optic nerve head in low tension glaucoma might be suspected. In the study presented here we have investigated patients presenting with the clinical diagnosis of low tension glaucoma. We used an improved method to check the widely accepted hypothesis of lowered pressure compliance of the optic nerve head in this condition.

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Subjects and methods

Seven consecutive patients (11 eyes) with low tension glaucoma were examined. The criteria for inclusion were: typical glaucomatous scotomas; intraocular pressure <21 mmHg; normal outflow facility; a cup/disc ratio >0·7.

Other diseases which might imitate low tension glaucoma (ischaemic optic neuropathy, intracranial tumours, etc.) were clinically excluded by *x*-rays of the skull, computer tomography, doppler sonography, and digital subtraction angiography of the carotid arteries. Three eyes out of our seven patients could not be examined, as visual acuity was below 20/200.

Three eyes in three patients with clearly delineated clinical ischaemic optic neuropathy were examined. For comparison, 10 healthy subjects (20 eyes) were investigated.

All groups were comparable in age and sex (Table 1). In all patients and healthy subjects no treatment affecting intraocular pressure was given. No mydriatics were used. The pressure compliance of the optic nerve head was tested by recording visual evoked responses under stepwise artificially increased intraocular pressures.

The following method was used to record the visual evoked responses. For monocular stimulation, checker board pattern reversal stimuli were applied (reversal rate 15 Hz, motion time 1·5 ms, luminance of the white checks 325 cd/m^2; luminance of the black checks 10 cd/m^2, angular subtense of a single check 27′ of arc; angular subtense of the projection screen 12°; the distance between the eye of the patient and the screen was 7 feet (2·1 m)).

In visual evoked response recording the different electrode was placed in the midline 5 cm above the inion and the reference electrode 30% (20/20 system) above the root of the nose. The common electrode was placed at the left ear lobe.

Table 1 *Distribution of persons by sex and by arithmetic mean of intraocular pressure and age*

	Low tension glaucoma	*Ischaemic optic neuropathy*	*Healthy subjects*
Eyes	11 eyes	3 eyes	20 eyes
Sex	3 males	1 male	5 males
	4 females	2 females	5 females
Intraocular pressure, mean	16·4 mmHg	17·5 mmHg	17·2 mmHg
Age, mean	58 years	63 years	60 years

Stimulation by this technique evokes potentials which appear in the steady state as signals at a frequency of 15 Hz, corresponding to the repetition frequency of the stimuli and in our measurements with amplitudes varying between 3 and 9 μV. These signals originate in the calcarine cortex.[10] The amplitudes of spontaneous brain potentials are much higher, and the signals we are interested in cannot be detected on an oscilloscopic display. The measurement of evoked signals is not easily done with commercial 'AC' meters or recording systems. Among several techniques which permit the detection and measurement of signals buried in noise we chose phase-sensitive or synchronous rectification. This method is based on the fact that the desired signals appear in synchronism with the stimulation frequency. The synchronous rectifier is basically a switch which permits the signals to pass during half of each period of the driving frequency. The passing signal current changes a condenser. The change in level is recorded as a function of time. The input resistance of the recorder discharges the condenser continuously. The combined effect of the charging and discharging leads to a recorded charge level which is proportional to the desired signals.

The spontaneous brain potentials have no component at the stimulation frequency. Thus their average value is zero. Their remaining contribution to the recorded signal is theoretically infinitely small. In practice it is kept insignificant by choosing the proper time constant for the recording system without making the response time too long. If there is a delay between the stimulation and the appearance of the evoked potentials, there is still synchronism with the stimulation frequency, but the phase of the evoked signal with respect to the stimulation signal is stuffed. If the phase shift approaches 90° or multiples of these, the evoked signals will not be recorded. Their average value is then zero. If we use a second synchronous rectifier with the same signal at the input but with a switching signal shifted by 90°, compared with the stimulation frequency (which can be easily done with a phase shifter) the phase shifted part of the evoked signal will be recorded in this second channel. It will be recorded at full amplitude if the phase shift is exactly 90°. For all evoked signals with intermediate phase shifts the time amplitude is calculated as the square root of the sum of the squares of the recorded signals with 0° and 90° phase shifts, as there will be components in both channels. The phase shift is found as the arc tangent of the ratio of the components with 0° and 90° phase shift.

The measuring and recording system can be considered as a unit and calibrated with signals which are injected into the electrode circuit connecting the electrodes on the patient with the measuring system. These signals can be varied in amplitude and phase and are derived from the stimulation frequency. In this way the calibration signal is automatically at all times in synchronism with the stimulation.

The test signal undergoes exactly the same treatment as the signals due to the evoked potentials.[11] In addition the test signal is covered by noise due to the spontaneous brain potentials and, possibly, external noise sources in the same way as the evoked signal. Thus any deterioration of the signals can be easily found and its effects can be exactly measured. The entire system can be tested at any time and faulty electrode connections spotted and corrected immediately.

The visual evoked responses were recorded monocularly without an artificial rise of intraocular pressure. Afterwards the intraocular pressure was increased stepwise artificially by the suction cup method[12] with a standardised suction cup.

The following pressure steps were applied: 80, 130, 160, 200, 250, 300, 350 mmHg of negative pressure. The conversion of the applied negative pressures to increased intraocular pressure (IOP) values involved use of the regression curves according to Hayatsu.[13-15] Because the regression curves were made for healthy eyes we applied a negative pressure by a suction cup in three patients with low tension glaucoma and in two patients with ischaemic optic neuropathy. We then measured the intraocular pressure by applanation tonometry. In this test we could not find any striking difference in the IOP values in the regression curves. We therefore feel justified in using the regression curves according to Hayatsu also in our patients with low tension glaucoma and ischaemic optic neuropathy.

The visual evoked response amplitudes were then plotted against the intraocular pressure.

Owing to the well known high variation of visual evoked response amplitude between individuals, the measured amplitudes are given as a percentage of the response amplitude of the visual evoked response recorded without artificially increased intraocular pressures, which is set as 100%. (The absolute values in microvolts are given in Table 2.)

Table 2 *Arithmetic mean and standard deviation of VER amplitudes*

	Low tension glaucoma	*Ischaemic optic neuropathy*	*Healthy subjects*
Maximum VER amplitude:			
mean	4·82 µV=100%	4·11 µV=100%	4·7 µV=100%
SD	±0·3 µV	±0·2 µV	±0·4 µV

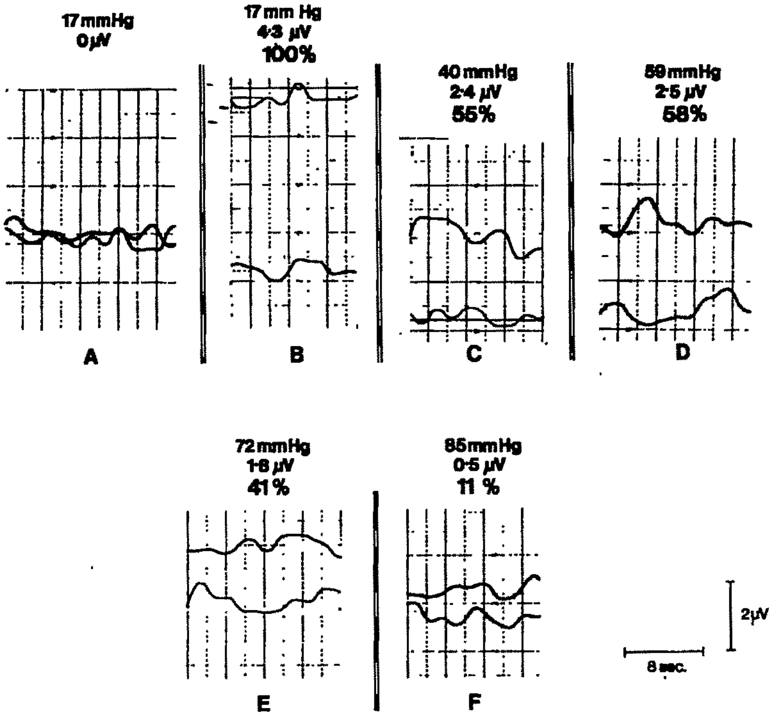

Fig. 1 *Original VER recordings of a healthy subject. The thick line represents the channel-1 output of the phase sensitive detector (PSD) and the thin line represents the channel 2 output. The phase angle between these two channels is exactly 90°. In the first recording (A) the checkerboard reversal is switched off, i.e., there is no stimulus. Thus recording A represents the baseline. In recordings B to F the checkerboard reversal stimulus is applied. Recordings A and B were registered at uninfluenced intraocular pressure (17 mmHg) and recordings C–F were registered at artificially increased intraocular pressures (40–85 mmHg). The deviations of the output recordings from the baseline (recording A) represents the output changes due to stimulation at uninfluenced intraocular pressure (recording B) and at artificially increased intraocular pressure (recordings C–F).*

Results

Figs. 1 and 2 show original recordings of the outputs of both channels on the strip chart recorder. Each recording section marked by an upper case letter shows the output of each channel during a time span of about 20 seconds. The sections were recorded successively. During certain intervals in the recording sections (marked by double lines) the subjects and the patients were allowed to generate artefacts by head movements. These intervals of about 10 seconds are not shown because they provide no information. For the recording sections A in Figs. 1 and 2 the subjects or patients looked at a checkerboard pattern which did not reverse—that is, the stimulus, the pattern reversal, was switched off. Thus the recording section A represents the base line. At the recording sections B in Figs. 1 and 2 the pattern reversal took place whereby the intraocular pressure was uninfluenced. The amplitude of the evoked potentials, indicated at each recording section below the intraocular pressure, is calculated from the absolute amplitude values as shown on the recordings and represents the normal value for the subject or the patient.

The intraocular pressure was artificially increased during the recording sections C through F in Fig. 1 and C through E in Fig. 2 respectively. The value of the intraocular pressure during these recording sections is given in the uppermost line above the recording sections. The calculated amplitudes are given below. We take the amplitudes of section B (at uninfluenced intraocular pressure) as the 100% value and indicate the amplitude values at increased intraocular pressure as percentages of the amplitude of Section B. The arithmetic mean and the standard deviation of the VER amplitudes are shown in Figs. 3, 4, and 5, plotted against the intraocular pressure. We measured only for certain pressure values. The curves shown in Figs. 3, 4, and 5 are called amplitude/pressure curves. They are drawn by connecting the measured points by straight lines.

The visual evoked response amplitudes plotted against the actual intraocular pressures of 20 healthy normotensive eyes are shown in Fig. 3. The slope of the curve is not uniform. For the first step increase of the intraocular pressure the amplitude is halved. The amplitude is almost constant for pressures up to 60 mmHg. It then decreases linearly to the residual noise level which is reached for a pressure of approximately 85 mmHg.

The amplitude/pressure curve (Fig. 4) for eyes with low tension glaucoma does not show an intermittent plateau. It decreases linearly to the noise level, which is reached at an intraocular pressure of 60 mmHg. In ischaemic optic neuropathy the amplitude pressure curve shows the intermittent plateau as seen in healthy subjects and reaches the noise level at about 80 mmHg intraocular pressure—a value similar to that in healthy subjects. The absolute visual evoked response amplitudes in microvolts are practically equal in healthy subjects and in patients with low tension glaucoma. The maximum amplitudes (Table 2) for patients with ischaemic optic neuropathy are approximately 0·75 µV lower than in the two other groups.

Discussion

The analysis of transient visual evoked potentials is

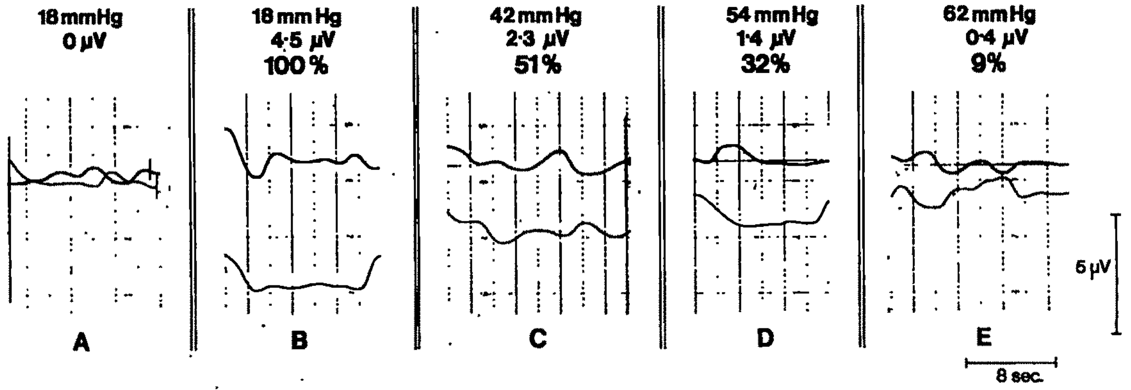

Fig. 2 *Original visual evoked response (VER) of a patient with low tension glaucoma (first row: intraocular pressure; second row: absolute VER amplitude in microvolts; third row: relative VER amplitude in percent). Recordings of the output from the phase sensitive detector. The thick line represents the output of channel 1 (phase angle 0°; CH_{a1}) and the thin line that of channel 2 (phase angle 90°; CH_{a2}). From the left: 1st recording (A)—base line from the unaffected eye (without stimulus). 2nd recording (B)—recording from the unaffected eye (checkerboard stimulus applied: reversal rate 15 Hz; motion time 1·5 ms; angular subtense of a single check 27' of arc). 3rd to 5th (C–E) recording—recordings with artificially increased intraocular pressures.*

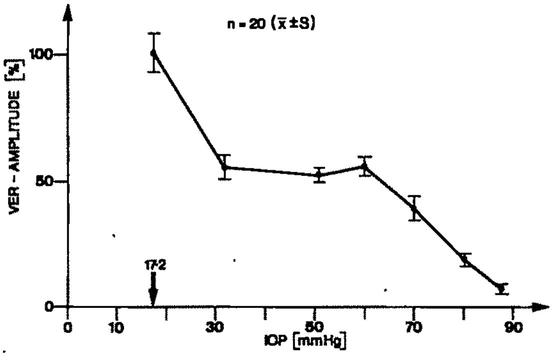

Fig. 3 *Visual evoked response amplitude of 20 healthy eyes plotted against the intraocular pressure. (17·2 mmHg=IOP of the unaffected eyes).*

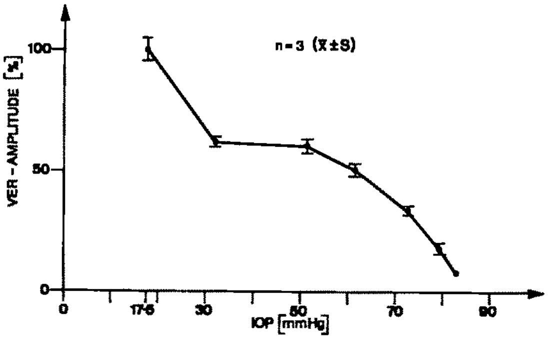

Fig. 5 *Visual evoked response amplitude of three eyes with ischaemic optic neuropathy plotted against the intraocular pressure. (17·5 mmHg=IOP of the unaffected eyes).*

today the most widely used method in clinical and experimental studies. It seems to provide the most information about the problems under investigation. Transient evoked potentials have the additional advantage that we can easily correlate the formation process and the results of measurement. However, the evaluation of transient visual evoked responses does have drawbacks. We bore in mind that the continuous recording of a transient visual evoked potential obtained with ordinary commercial instruments contains no information on the effects of input noise. This information, however, is important:

Transient evoked potential curves are a sequence of arithmetic means. The information content of an arithmetic mean is limited if the distribution of the single values is not known.[16] In recording transient evoked potentials it is in addition assumed that the noise of the disturbing signals is 'white'. This is not true: Stodtmeister *et al.*[17] showed that the transient evoked potentials are to some extent influenced by forced synchronisation of the alpha rhythm.

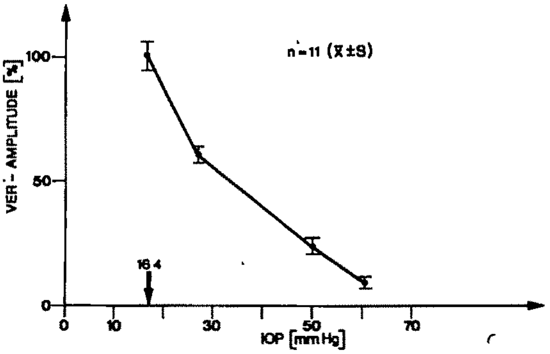

Fig. 4 *Visual evoked response amplitude of 11 eyes with low tension glaucoma plotted against the intraocular pressure. (16·4 mmHg=IOP of the unaffected eyes).*

A further problem with transient evoked potentials is that the recording time is relatively long (approximately 30–60 seconds). In this study we recorded the visual evoked potentials by a fast method because artificial increase in intraocular pressure accelerates the outflow of aqeuous humour. The method of phase sensitive detection has been used by other authors quite successfully.[18-20] Regan[20] has pointed out in a basic article that the analysis of steady state evoked potentials by phase sensitive detection is a very suitable tool for evaluating the function of the visual system. We used this method because it is fast and more sensitive than averaging methods, and the measurement is straightforward. An additional reason for using this method is that the influence of the noise on the signals can be derived from the recordings, and a special advantage of it is the ease of calibration of the entire system, including the electrodes. Thus we believe that phase sensitive detection is a valuable and trustworthy tool in the clinical examination of patients for glaucoma. Owing to individual anatomical conditions the position of the macular projection in the calcarine cortex differs slightly in each individual. This causes considerable differences between individuals in the amplitudes of the visual evoked responses. We have taken the quiescent amplitude as 100% for each amplitude/pressure curve and expressed the remaining values as a percentage of the quiescent values. The relative amplitude/pressure curves are quite uniform for the different groups which we examined.

The visual evoked response amplitudes as a sign of optic nerve head function do not decrease continually (Fig. 3) but remain almost constant for an intermediate pressure range. We have described this behaviour in younger subjects,[21 22] and we observed it also in the older subjects presented here. The plateau in the amplitude/intraocular pressure curve has been interpreted as an indication of autoregulation. We therefore assume that autoregulation still works in healthy subjects of a more advanced age. The patients with low tension glaucoma, however, do not show this plateau in the amplitude/pressure curve, whereas those patients with ischaemic optic neuropathy do show an intermittent plateau. This result leads to the conclusion that there are two different pathogenetic processes in these two diseases, which are not always clinically distinguishable.

Anderson[23] mentioned difficulties in attempting to explain low tension glaucoma with respect to primary open angle glaucoma. This is because in low-tension glaucoma there is no increased intraocular pressure which may lead to a mechanically induced damage of the optic nerve head. But the damage in low tension glaucoma and in primary open angle glaucoma is comparable. Therefore Anderson[23] suggests a lack of autoregulation in primary open angle glaucoma and in low tension glaucoma as the common pathogenetic factor. There is an increasing amount of evidence that auroregulation of ocular blood flow in the optic nerve head takes place. It can be demonstrated by different methods and in different species as well as in man.[24–27]

The lack of autoregulation has been suggested by Anderson[23] and by Robert and Maurer[26] as a pathogenetic factor in the development of damage in low tension glaucoma and primary open angle glaucoma. From our results we consider that such lack of autoregulation can be confirmed. Furthermore, the amplitude/intraocular pressure curves in low tension glaucoma, ischaemic optic neuropathy, and in healthy subjects do not differ only in relation to autoregulation.

It can also be seen that the critical pressure in low tension glaucoma is reached at lower intraocular pressure values than in patients with ischaemic optic neuropathy and healthy subjects. In this context we define 'critical pressure' as that pressure for which visual evoked response amplitudes reach the noise level. In our recording system the base line noise is about 300 nanovolts, corresponding to about 10% of the initial visual evoked response amplitude. Thus this low critical intraocular pressure and the lack of autoregulation described can be interpreted as a lowered pressure compliance of the optic nerve head in low tension glaucoma, and this lowered pressure compliance may be the origin of optic nerve damage.

Comparison of the critical intraocular pressures in low tension glaucoma and in ischaemic optic neuropathy shows that this pressure is higher in ischaemic optic neuropathy than in low tension glaucoma (Figs. 4 and 5). This result confirms the suggestion, backed by clinical experience, that low tension glaucoma and ischaemic optic neuropathy are distinct entities.

Previous results[21 22] have shown that in patients with primary open angle glaucoma there is no sign of autoregulation in the VER amplitude/pressure curves. This finding appears to be similar to those presented here in patients with low tension glaucoma. But the 'critical pressure'—that is, the intraocular pressure for which the visual evoked response amplitudes disappear in the noise—corresponds in these cases to an intraocular pressure of about 80 mmHg. Thus the suggestion is confirmed that primary open angle glaucoma and low tension glaucoma are the same disease, but in low tension glaucoma the 'critical pressure' is lower, which means that the pressure compliance of the optic nerve head is lower.

According to Richardson[28] 'it is probably best to assume—as with most human ailments—glaucoma will prove to be a disease where lack of resistance to force is more important than the force itself.' Previous results[21 22] and those reported here may be interpreted in the same way. We believe that the 'lack of resistance' noted by Richardson can be confirmed by the methods used here.

Referring to animal studies Sossi and Anderson[25] and Anderson and Davis[29] supposed that an important factor in glaucoma damage is the lack of autoregulation. Our results show that the lack of autoregulation is an important factor in low tension glaucoma. It is widely suspected that the pressure compliance of the optic nerve head is lowered in low tension glaucoma. We believe that it is possible to carry out a clinically practicable determination of this lowered pressure compliance by the method used here.

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Laser trabeculoplasty as supplementary treatment for primary open angle glaucoma

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SUMMARY A prospective trial was conducted of laser trabeculoplasty randomly assigned to one eye of a group of elderly patients with bilateral primary phakic open angle glaucoma who were already taking the maximum medical treatment that they could tolerate. With a minimum follow-up of 2½ years (mean 35 months) a significant fall in mean intraocular pressure of over 7 mmHg (30%) at the time of the patient's last visit was noted in the treated eye.

Surgery and medical therapy have been employed since the 19th century to lower intraocular pressure in patients with glaucoma, but in the past few years argon laser therapy has gradually been gaining acceptance as a new method of treatment either to supplement or to replace these options.

Initially in the early 1970s a high intensity laser beam was used to perforate the trabecular meshwork and enter the canal of Schlemm.[1] This approach achieved only a temporary pressure reduction because of the healing of the micropuncture sites. It was subsequently found that extensive laser application to the anterior chamber angle in monkeys could actually induce glaucoma.[2] In 1979, however, a different approach was proposed.[3,4] By using the argon laser with a far lower power setting so as to induce contraction rather than puncture of the collagen in the trabecular meshwork, a much longer-lasting reduction of intraocular pressure was achieved. Following this[3] and other[5-7] encouraging reports from the USA a prospective trial was set up at the Glaucoma Unit, Moorfields Eye Hospital, to investigate the effects of laser trabeculoplasty in a discrete, but clinically the most common, group—namely, elderly patients with primary chronic open angle glaucoma.

Patients and methods

A highly defined group of elderly patients was selected according to the following criteria:

(*a*) Bilateral primary open angle (simple) glaucoma as judged by elevation of intraocular pressure (above 21 mmHg), glaucomatous disc change, and visual field loss.

(*b*) No previous eye surgery nor evidence of other eye disease.

(*c*) Patients already taking in both eyes the maximum antiglaucoma medication that could be tolerated (Fig. 1). In most cases this would have been a minimum of two and a maximum of four antiglaucoma medicines (timolol, pilocarpine, sympathomimetics, and acetazolamide in varying combinations). Yet despite this treatment the intraocular pressure was consistently exceeding 21 mmHg and considered to be inadequately controlled.

Before laser treatment was given a baseline ophthalmological examination was performed and full history recorded. The 'initial intraocular

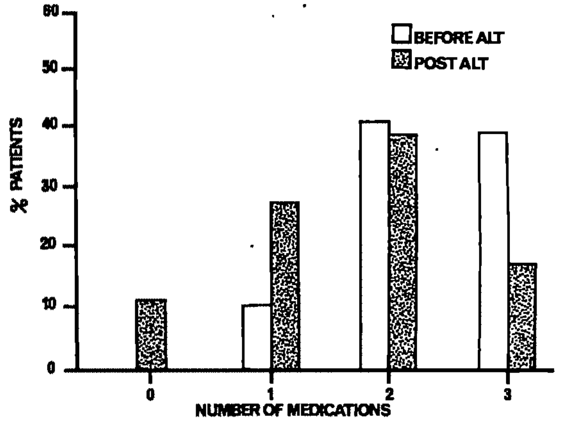

Fig. 1 *Reduction in medication after laser treatment. ALT=argon laser treatment.*

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pressure' in each eye, by means of a Goldmann applanation tonometer, was taken as the average pressure of the last three clinic visits. One eye was then randomly selected by computer for laser therapy, the other eye acting as a control.

The laser trabeculoplasty consisted of a single outpatient sitting at which 100 evenly spaced, low intensity burns 0·1 second duration were applied with a continuous wave argon laser (Laser Tek) and Goldmann three-mirror contact lens, to the 360° of the midtrabecular meshwork.[8]

In the first six patients a spot size of 350 µm was chosen; and for the remainder 150 µm was employed because of difficulties in focusing the larger 350 µm spot. The power was adjusted for each individual to give an endpoint of blanching and minimal vaporisation bubbling. It was found that a power setting of 0·5 to 1 watt was usually sufficient.

After laser treatment the previous maximum tolerated medical therapy was continued to *both* eyes and, in addition to the treated eye only, prednisolone drops 0·1% qid were added for about one week. The patients were reviewed on a regular basis, initially at frequent intervals and then later every three months. Nearly all the postlaser tonometry readings were checked by two independent observers, one of whom was a glaucoma technician who had no knowledge of which eye had received the argon laser trabeculoplasty. The glaucoma visual fields were also assessed by two observers, one of whom was the senior glaucoma field technician, and who again was unaware of the patient's past laser history.

It was decided at the outset of the trial that, if the laser treatment produced a persistent lowering of IOP lasting for one year, the same treatment would be offered to the 'untreated' eye. At the same time an attempt would be made to withdraw some or all of the antiglaucoma treatment given to the 'treated eye'.

Results

Twenty-five patients were initially included in the study; their mean age was 72·5 years at the start (range 56 to 90). Of these, one died six months after laser treatment and was excluded, though his intraocular pressure had fallen from a baseline of 22 mmHg to 16 mmHg at his last reading. The 24 surviving patients had a minimum follow-up of 2½ years (range 30 to 40 months, mean 35 months). One patient was committed to an institution with senile dementia and his condition was such that it was impossible to obtain accurate visual fields, though his intraocular pressures have been followed up.

Before laser trabeculoplasty the mean intraocular pressures on treatment were similar in the laser treated and untreated eyes (23·8 mmHg). After laser treatment there was, by one month, a significant fall in the mean pressure in the treated eye which has largely been maintained. A transient initial fall in the untreated eye was also seen (Table 1, Fig. 2).

After one year attempts were made to reduce the medication as far as possible in the treated eye while still maintaining adequate control of the glaucoma. Three of the 24 surviving patients (13%) were able to

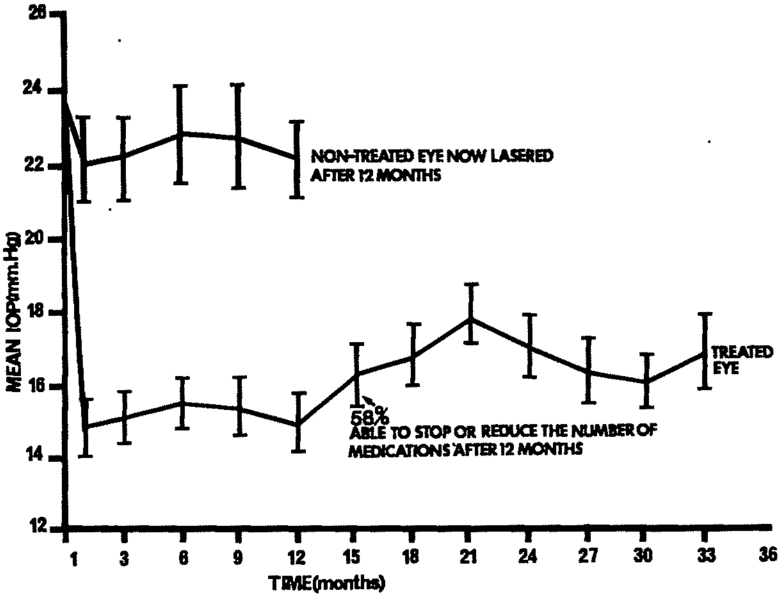

Fig. 2 *Intraocular pressure changes plotted against time in patients receiving laser trabeculoplasty compared with those not receiving laser trabeculoplasty for the first one year of the Study.*

Table 1 *Comparison of intraocular pressure in patients after laser trabeculoplasty to one eye*

Time (months)	*No. of patients*	*Lasered eye mean intraocular pressure (mmHg)*	*Non-lasered eye mean intraocular pressure (mmHg)*	*Comparison of mean intraocular pressure non-lasered to lasered eye*	*p Value*
Baseline	24	23·8	23·8	0	—
1	24	14·9	22·0	7·1	<0·001
3	24	15·1	22·2	7·1	<0·001
6	24	15·5	22·8	7·3	<0·001
9	24	15·4	22·7	7·3	<0·001
12	23*	15·0	22·1	7·1	<0·001
15	23*	16·3			
18	23†	16·7			
21	24	17·8			
24	24	17·0			
27	24	16·3			
30	23‡	16·0			
33	17	16·8			
36	8	18·6			

*One patient with irregular follow-up at this time.

†Irregular follow-up at this stage in patient institutionalised with senile dementia.

‡One patient underwent trabeculectomy surgery at 27 months after argon laser trabeculoplasty.

stop all treatment, while a further 11 (46%) came off some of their medications. One patient, who was a poor complier, had acetazolamide tablets added to his baseline eyedrop regimen. The mean number of different antiglaucoma medications taken before laser treatment was 2·3 per patient and at their last visit 1·6 per patient (Fig. 1).

Nineteen of the 23 (83%) patients in whom it has been possible to obtain Goldmann visual field analyses have maintained stable visual fields. Of the remaining four cases two have shown slight field progression despite intraocular pressures constantly recorded below 21 mmHg (mean intraocular pressure 12 mmHg and 18 mmHg respectively). However, these findings did not differ significantly from the visual field changes seen in the control eye.

If success of laser treatment is defined in intraocular pressure terms as (*a*) a fall of intraocular pressure of at least 20% from baseline (mean of last three readings) and in addition (*b*) no intraocular pressure readings above 21 mmHg, then treatment in 19 of the 24 patients (79%) was a success with a minimum follow-up of 2½ years. Of the five failures by the above criteria three failed after one year ('late failures'), and one of these required filtration surgery at 27 months after argon laser trabeculoplasty.

Discussion

Argon laser trabeculoplasty was able to produce a clinically useful fall in intraocular pressure of more than 7 mmHg (30%) in this group of elderly patients with chronic simple glaucoma who were already taking the maximum medical therapy that they could tolerate. In over 80% of patients no further loss of visual field has occurred so far, though this did not differ significantly from the control group. (It has to be remembered that the intraocular pressures in these control eyes remained in excess of 21 mmHg only for the first 12 months of the study, after which time these eyes too would have been treated with laser trabeculoplasty.)

The eyes treated in this study received laser energy to 360° of the trabecular meshwork at one time. More recent work has shown that this treatment could result in a temporary increase of intraocular pressure.[9] We now give the same 360° treatment in two separate sessions, treating one half of the trabecular meshwork each time, and immediately after each session instil pilocarpine in an attempt to minimise any transient ocular hypertension.

Wise and Witter's original description recommended the use of a spot size of 50 µm.[3] In-vitro studies suggest that a larger spot size may be more efficacious.[10] A clinical study comparing the use of different spot sizes supports this view (Lattimer and Hitchings, in preparation). The results obtained by our technique using 150 µm spots size certainly compare well with those obtained by others.[5-7]

During the first year of the study the intraocular pressures in the 'control' group showed a marked fall over the first one to two months (Fig. 2). We considered that this was a placebo effect, for the intraocular pressures in this group then rose to the prestudy levels without any alterations in medication having taken place. We consider that this response highlights the importance of restricting the number of variables in a prospective clinical study. After one year of follow-up, as Fig. 2 shows, a steady state in intraocular pressure levels had been reached. Thus it was considered reasonable not only to treat the control group with laser but also to try to withdraw antiglaucoma medicines from the treated group.

The good results of laser trabeculoplasty in patients who are already on a full medical regimen led to the idea of using the laser earlier in the disease process and indeed as the primary treatment of certain types of glaucoma. Studies are already under way to investigate this possible new role for laser therapy in the management of primary open angle glaucoma, and preliminary results are encouraging.[8 11 12]

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Use of contrast sensitivity measurement in the detection of subclinical ethambutol toxic optic neuropathy

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SUMMARY Contrast sensitivity was measured by means of Arden grating plates in 100 patients on medication for pulmonary tuberculosis. The scores were abnormal in 38·2% of the patients whose therapy included ethambutol for three months, and 36·7% of the patients on similar treatment for six months. In comparison with age matched groups of patients on a regimen where streptomycin replaced ethambutol a statistically significant number of the patients on ethambutol had abnormal scores. This study suggests that Arden contrast sensitivity plates would be effective in detecting subclinical toxic optic neuropathy due to ethambutol and therefore could be used for routine monitoring of ocular function of patients on ethambutol. Loss of contrast sensitivity may explain why some patients on ethambutol with normal visual acuity and colour perception may still complain of visual disturbance.

Ethambutol hydrochloride is an orally administered agent specifically effective against *Mycobacterium tuberculosis*. Carr and Henkind[1] initially reported optic nerve toxicity due to ethambutol in 1962, and further reports have established this side effect as a dose related retrobulbar optic neuropathy.[2] In most studies it appears that the degree of reversibility depends on early recognition of symptoms and signs of ocular toxicity.[3]

Since the introduction by Arden[4] of a series of contrast gratings of various spatial frequencies, contrast sensitivity has been used to assess visual function in a number of ocular diseases. In particular the Arden contrast sensitivity test has been used to assess visual function in diseases involving the optic nerve, for example, in chronic glaucoma[5] and optic neuritis.[6] This suggested that the Arden test might be useful in the early detection of ethambutol toxic optic neuropathy. It was also thought that an isolated loss of contrast sensitivity might explain why some patients on ethambutol with normal visual acuity and colour perception may still complain of visual disturbance.

Patients and methods

We examined 100 black inpatients suffering from pulmonary tuberculosis. Acid-fast bacilli had been identified in their sputa and chest *x*-rays were suggestive of tuberculosis. There were 38 females and 62 males.

At this tuberculosis hospital two medication regimens are used in the treatment of pulmonary tuberculosis. Patients on schedule 1 receive streptomycin 1 g daily, rifampicin 450 mg daily, and isoniazide 400 mg daily for six months and pyrazinamide 2 g daily for three months. When streptomycin cannot be administered, schedule 2 is used, which differs from schedule 1 in only one respect, in that ethambutol 25 mg/kg is given daily in place of streptomycin. As a general rule the younger patients are placed on schedule 1 and the older patients on schedule 2. Patients undergo a routine chest *x*-ray after three months and again after six months. After a full six-month period of treatment patients are discharged and followed up as outpatients.

This established policy conveniently allowed us to examine four groups of patients. These groups were based on whether the patient had received ethambutol or not, for a three-month or a six-month period. Groups 1 and 2 were patients receiving schedule 2 medication, and groups 3 and 4 were patients on schedule 1 medication. Group 1, 34 patients (mean age 40 years, range 23–63), had received ethambutol for three months; while group 2,

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30 patients (mean age 45 years; range 20–83), had received ethambutol for six months. Group 3, 22 patients (mean age 32 years, range 18–44), had received no ethambutol for three months; and group 4, 14 patients (mean age 31 years; range 19–43, had received no ethambutol for six months.

We further subdivided these four groups to enable us to compare age matched groups. The results of patients between the ages of 20 and 49 years (3rd, 4th, and 5th decades) were analysed. Group A (a subdivision of group 1) consisted of 26 patients with a mean age of 35·3 years (range 23–49); group B (a subdivision of group 2), 15 patients, with a mean age of 32·1 years (range 20–48); group C (a subdivision of group 3), 21 patients, with a mean age of 32·7 years (range 22–44), and group D (a subdivision of group 4), 13 patients, with a mean age of 31·3 years (range 20–42).

The patients were examined the day before their routine chest *x*-ray. Visual acuity was tested at distance and at near; colour vision was assessed (Ishihara's test), and ophthalmoscopy was performed. Patients with obvious eye disease were excluded from the study. (This meant that several patients with cataracts and two patients with chronic glaucoma were excluded.) An independent examination of the patient's contrast sensitivity was carried out with Arden contrast sensitivity plates by the method described by Arden.[4] Each eye was scored separately, and for each eye a total score consisting of the sum of the scores on each of the six plates was determined. A total score of more than 82 was considered abnormal,[4] and for analysis the lower score of the two eyes was used.

Results

The mean score of patients in group 1 was 80·3 and 38·2% had a total contrast sensitivity score of more than 82. This contrasted with patients in group 3, where the mean score was 63·0 and where 9% scored more than 82. There is a significant difference between the scores in these two groups ($p<0{\cdot}005$ paired *t* test; $p<0{\cdot}015$ by Fisher's exact test). The patients in group 2 had a mean score of 79·2, while 36·7% scored more than 82, compared with those patients in group 4, where the mean score was 62·0 and 7·1% scored more than 82. Once again these differences are statistically significant ($p<0{\cdot}025$ by paired *t* test; $p<0{\cdot}04$ by Fisher's exact test) (Table 1).

When the sex of the patients whose medication included ethambutol is considered, the mean age of the females was 41·5 years and the males 44·4 years (statistically comparable ages). Of the patients on ethambutol who scored more than 82, 44% were females and 33% were males. This difference, however, is not statistically significant (Table 2).

The histogram in Fig. 1 is an analysis of the 100 patients divided by age in decades. Statistically there is no difference between the mean age of the four groups of patients between the ages of 20 and 49. In group A 34·6% scored more than 82, and in group B 28·6% were abnormal. In group C 9·5% were abnormal, and in group D 7·7% were abnormal. On statistical analysis a significant number of patients on ethambutol scored more than 82, compared with those not on ethambutol ($p<0{\cdot}015$ by Fisher's exact test). The mean scores were also significantly higher for patients on ethambutol ($p<0{\cdot}005$ by paired *t* test) (Table 3).

When the patients between the ages of 20 and 49 who scored less than 83 were assessed, the mean scores of patients on ethambutol were similar to the mean scores of patients not on ethambutol. The 28 patients in groups A and B (mean age 33·1 years) had a mean score of 62·2 compared with the 31 patients in groups C and D (mean age 31·6 years) with a mean score of 59·8. There is no statistically significant difference between the mean scores of patients who scored less than 83, irrespective of whether they received ethambutol or not (Table 4).

In a comparison of the patients who were on ethambutol who scored more than 82, the mean score of abnormal patients in group 1 who had received ethambutol for three months was 105·6 (standard deviation 19·1), while for abnormal patients in group 2 who had received ethambutol for six months the mean score was 110·4 (standard deviation 16·8). There is no statistically significant difference between the scores of these two groups.

When the age matched groups are considered, no single spatial frequency was particularly effective in detecting the effect of ethambutol on the optic nerve.

Table 1 *Contrast sensitivity scores >82 and mean Arden grating scores*

	n	*>82*	*Mean*	*SD*
Group 1 Three months on ethambutol	34	13	80·3	25·4
Group 2 Six months on ethambutol	30	11	79·2	27·6
Group 3 Three months not on ethambutol	22	2	63·0	17·8
Group 4 Six months not on ethambutol	14	1	62·1	14·1

Table 2 *Sex distribution of patients with contrast sensitivity scores >82*

		Female		*Male*	
		n	*>82*	*n*	*>82*
Group 1	Three months on ethambutol	14	6	20	7
Group 2	Six months on ethambutol	11	5	19	6
Group 3 and 4	Not on ethambutol	13	2	23	1

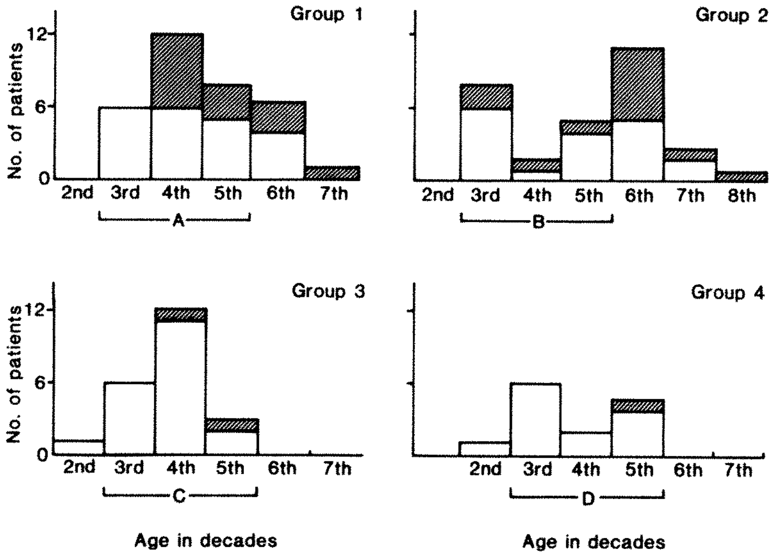

Fig. 1 *Histogram of 100 patients, divided by age in decades. Hatched areas show numbers of patients scoring more than 82. Clear areas show numbers of patients scoring 82 or less.*

The estimate of reliability using one spatial frequency was 0·6702133, while the estimate of reliability using all six spatial frequencies was 0·9242056.

Of this group of 100 patients five on ethambutol had a partial decrease in colour perception, with a contrast sensitivity score of more than 82. One of these patients had a reduction in Snellen acuity (R 6/9, L 6/12 best corrected). No abnormalities of their optic discs were observed. The remainder of the patients on ethambutol, including those with abnormal contrast sensitivity, and all the patients on streptomycin in place of ethambutol, had normal visual acuity, colour perception (Ishihara), and discs.

Discussion

Ethambutol, a dextrorotatory isomer of 2,2′-(ethylenedimino)-di-1-butanol, is a widely used oral agent effective against mycobacteria. Since its introduction in 1961 the clinical effectiveness and toxicity have been comprehensively documented.[7,8] The drug is well tolerated, although side effects like numbness in the lower limbs, nausea, and other gastrointestinal upsets have been described[8]. The major side effect is a dose-related retrobulbar neuropathy. Leibold[2] reported that in 59 patients treated with 35 mg/kg ethambutol per day optic neuropathy was seen in 18% of the patients. At 25 mg/kg per day the incidence of toxicity dropped to 2·25%. Citron[3] confirmed this low risk, finding an incidence of optic neuropathy of 6% among 34 patients receiving 25 mg/kg per day.

The ocular toxicity may have two forms, and it usually affects both eyes. Patients with central or 'axial' toxic effects have reduced visual acuity, impaired colour vision (especially on the red-green axis), and a central scotoma. Those with 'periaxial' toxic effects have a defect in peripheral isoptres of their visual field, with little or no decrease in visual acuity and normal colour vision. Most studies suggest that the neuritis is reversible if the drug is stopped and that the speed of recovery depends on early recognition of symptoms and signs.[3]

The exact mechanism by which ethambutol produces retrobulbar neuritis is unknown. Experimentally in animals it has been shown that the drug can cause depletion of copper and zinc, with a decrease in cytochrome C oxidase activity.[9] A relationship between these changes and ocular toxicity has not been established. It has also been suggested that, being a butanol derivative, ethambutol may cause toxic amblyopia by the same mechanism as alcohol.[10]

Table 3 *Contrast sensitivity scores >82, ages 20–49, and mean Arden grating scores*

		n	*>82*	*Mean age*	*Mean*	*SD*
Group A	Three months on ethambutol	26	9	35·3 yr	78·8	25·5
Group B	Six months on ethambutol	15	4	32·1 yr	72·9	24·7
Group C	Three months not on ethambutol	21	2	32·7 yr	63·9	17·7
Group D	Six months not on ethambutol	13	1	31·3 yr	61·3	14·4

Table 4 *Contrast sensitivity scores <83, ages 20–49, and mean Arden grating scores*

	n	*Mean age*	*Mean*	*SD*
Group A Three months on ethambutol	17	33·6 yr	63·4	12·2
Group B Six months on ethambutol	11	32·4 yr	60·5	12·8
Group C Three months not on ethambutol	19	32·4 yr	60·1	13·7
Group D Six months not on ethambutol	12	30·3 yr	59·3	12·8

Schmidt,[11] using high doses of ethambutol on monkeys (800 mg/kg) found demyelination of the optic nerve fibres.

There are two methods of reducing the risk of ethambutol induced toxic optic neuropathy. Firstly, the dose could be reduced to 15 mg/kg per day.[12] Secondly, the visual function of patients on ethambutol should be carefully assessed. Saroux *et al.*[13] recommended a monthly check with a Farnsworth-Munsell colour test, while Leibold[2] recommended regular visual acuities and visual field checks.

The use of routine visual tests during treatment is not optimal, because visual acuity, colour perception, fields, and optic discs may be normal in the presence of subjective visual disturbance[3]. It appeared from our study that only five patients (7·8%) might have been considered to have optic nerve disease by simple screening tests.

Yiannikas *et al.*[14] recently suggested that visual evoked potentials would be useful in detecting subclinical disturbances in optic nerve condition. They examined 14 patients all receiving less than 30 mg/kg ethambutol per day. In six patients (43%) the VEP showed changes in latency and amplitude of the P 100 component at the one- or three-month interval. Five of these six patients did not have other changes in visual function as measured with clinical neuro-ophthalmological examination.

Since Arden[4] introduced a rapid and simple method of testing contrast sensitivity, it has become clear that isolated loss of contrast sensitivity exists in certain diseases, and in many others loss of contrast sensitivity is more prominent and disturbing to the patient than the loss of visual acuity.

Using this test, Arden reported a normal population mean score of 69·8, and suggested that a patient scoring more than 82 should be considered abnormal. Because the values obtained from these plates are dependent on the tester, who must uncover the sheets at a constant speed, the results given in this paper are not directly applicable to all clinicians using the test. Our normal patients, however, scored a mean of 60·9, so any patient scoring more than 82 would be significantly abnormal. We found that 38·2% of the patients whose therapy included ethambutol for three months and 36·7% of the patients on similar treatment for six months had abnormal scores.

Because contrast sensitivity decreases significantly with age,[15,16] we compared four age matched groups of patients. Once again a statistically significant number of the patients whose medication included ethambutol had abnormal scores. Of the patients in the 3rd, 4th, and 5th decades of life, 34·6% were abnormal after three months and 28·6% abnormal after six months of ethambutol. 9·5% of the patients in the 3rd, 4th, and 5th decades who were not on ethambutol were abnormal after three months and 7·7% abnormal after six months. The three patients not on ethambutol who had abnormal contrast sensitivity scores were on a schedule that included streptomycin, isoniazide, rifampicin, and pyrazinamide. Two of these patients had normal eyes, and one was a corrected high myope who did not appear to have macular pathology on funduscopy. None had received previous tuberculosis treatment. The explanation for this finding may be that both isoniazide and streptomycin are optic nerve toxins, and, although use of either of these agents with ethambutol may lower the toxic threshhold, they may be toxic on their own.[17,18]

It has previously been reported that the toxic optic neuropathy secondary to ethambutol appears only after a latent period of 77 to 313 days following the beginning of treatment.[12] It might therefore have been expected that more patients would be abnormal at six months than at three months. A possible reason why an almost similar number of patients had abnormal contrast sensitivity at three and six months (with similar mean scores) could be the fact that all the patients gained weight while in hospital. The ethambutol dose was kept constant for the entire six-month period, so the mg/kg dose gradually fell over this period to a mean dose of 22 mg/kg per day at six months.

The potential severity of ocular toxicity attributed to ethambutol, and the reversibility of the reaction when the drug is stopped, necessitate a screening procedure capable of detecting ocular toxic effects before a deficit occurs. It would appear that, for routine monitoring of ocular function of patients on ethambutol, Arden contrast sensitivity plates would be simple and effective. However, further study is required using serial testing in individual patients, in an attempt to disclose the onset of ethambutol toxic optic neuropathy and to establish the precise place of the test in the management of these patients. Loss of contrast sensitivity may explain why some patients on tuberculosis treatment who have normal visual acuity and colour perception may still complain of visual disturbance.

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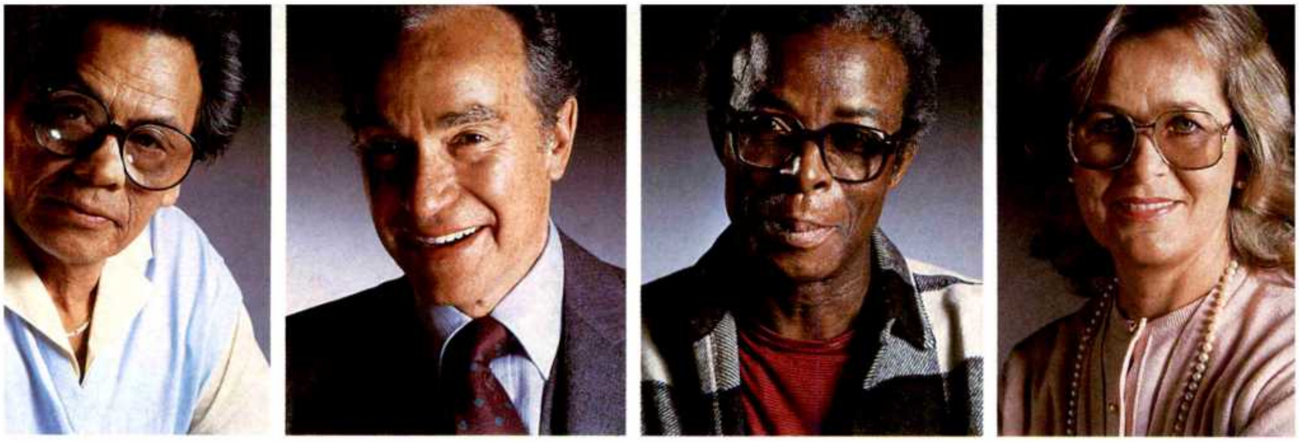
For abridged product information, see page 4.



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British Journal of Ophthalmology, 1987, 71, 197–200

Basal iridectomy at 6 o'clock in the aphakic eye treated with silicone oil: prevention of keratopathy and secondary glaucoma

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SUMMARY In the aphakic eye, with intact iris diaphragm, silicone oil has frequently caused a pupillary block. In this situation aqueous humour accumulates behind the iris and forces silicone oil through the pupil into the anterior chamber. An iridectomy at the 6 o'clock position can effectively prevent this pupillary block. The iridectomy allows free passage of aqueous to the anterior chamber which remains free of silicone oil. No permanent contact with silicone oil and the cornea is established, and development of keratopathy is prevented. The effect of this iridectomy in 62 eyes with intact iris diaphragm in patients in Rotterdam (35 cases) and Nagoya (27 cases) is demonstrated. Only in 6·5% of the cases was silicone oil present in the anterior chamber at the end of the follow-up period of 7 months.

Intraocular silicone oil is used for the repair and support of complicated cases of retinal detachment.[1-5] Complications of silicone oil implantation in detachment surgery have been described.[1 6-8] Glaucoma,[4 9] cataract,[9 10] and corneal opacification[10-14] are the problems that are encountered most frequently. In the aphakic eye both increased intraocular pressure and corneal opacification may present as serious complications, especially when silicone oil is in permanent contact with the corneal endothelium and chamber angle. Silicone oil keratopathy has been described by us earlier.[12]

This paper describes the advantageous effect of an iridectomy at the 6 o'clock position in the intracapsular aphakic eye to ensure aqueous circulation from the posterior segment to the anterior chamber. Ando started this prevention of pupillary block and thus gave us a solution to separate the silicone oil from the cornea and chamber angle in aphakes.[15]

The results of the 6 o'clock iridectomy in 35 patients treated in Rotterdam, The Netherlands, and 27 patients treated in Nagoya, Japan, are described. For comparison we present the fate of the cornea in 16 patients whose intracapsular aphakic eye had been treated with silicone oil injection and did not have an iridectomy at 6 o'clock. These 16 patients were operated on during the half year preceding the introduction of the 6 o'clock iridectomy.

Patients and methods

All 62 patients were aphakic at the time of silicone oil injection, had sufficient iris diaphragm left to perform a 6 o'clock iridectomy, and were available for follow-up during the full postoperative period or until the silicone oil was removed from the eye. Patients with an inferior coloboma, aniridia, or incomplete follow-up were excluded from the study. In all patients the iridectomy was performed during the months January to October 1984.

The patients were treated with intraocular silicone oil (1000 cS) for the management of complicated retinal detachment. All patients either had proliferative vitreoretinopathy (PVR), giant tears, or both. Most patients had had previous detachment surgery. In all cases the iridectomy was made at the time of first injection of silicone oil in these aphakic eyes. In 10 cases (Rotterdam three, Nagoya seven) a pars plana lensectomy or intracapsular extraction via a

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corneal incision was performed at the time of surgery. In all other cases the eyes that underwent silicone oil injection and iridectomy at 6 o'clock were aphakic at the time of surgery.

The 6 o'clock iridectomy was performed after the vitrectomy had been completed. The iris base was gently aspirated from the vitreous side into the porthole of the vitrectome and a hole was made. The size of the iridectomy, depending on the shape of the diaphragm, was at least 2 mm in diameter.

After the vitrectomy and iridectomy, silicone injection was started through the infusion canula in the pars plana. Slow expansion of the oil bubble caused the anterior chamber fluid to be trapped in front of the iris. Sufficient endodrainage by modified flute needle[16] created space for the pump-driven, footswitch-operated silicone oil injection. The optic nerve vessels were carefully checked for pulsations to prevent pressure rises during silicone oil injection. This also helped to maintain a normal anterior chamber filled with 'aqueous'.

If any oil entered the anterior chamber during injection the surgeon continued the oil injection. Aqueous was drained with a flute needle from the posterior segment until the eye was almost completely filled with oil. Then the anterior chamber was entered by a small canula through the pars plana and through the iridectomy to force the oil down behind the diaphragm with injection of aqueous substitute.

By this method we were generally able to achieve an anterior chamber free from oil at the conclusion of the operation.

Results

The results are summarised in Table 1.

The Rotterdam material consisted of 35 patients (35 eyes). The mean observation time was 7·5 months (ranging from 3 to 14 months). Of 35 cases 33 had a silicone oil face at the level of the pupil or what was left of the diaphragm. At the end of the observation period silicone oil was present in the anterior chamber in contact with the corneal endothelium in two cases.

Table 1 *The cornea and silicone oil: results of 6 o'clock iridectomy in intracapsular aphakic silicone oil surgery*

	Rotterdam	*Nagoya*	*Total*	*%*
Number of cases	*35*	*27*	*62*	*100*
Oil in anterior chamber	2	2	4	6·5
Iridectomy initially closed	6	4	10	16·1
Iridectomy permanently closed	5	4	9	14·5
IOP>21 mmHg without medication	5	4	9	14·5
IOP>21 mmHg with medication	0	0	0	0
Corneal opacification	2	4	6	9·7

In one of these two cases the iridectomy had closed at three months postoperatively for unknown reasons, and the intraocular pressure was raised to 25 mmHg. The condition of the posterior segment allowed oil removal after six months. The visual acuity of this eye that had PVR in high myopia remained 0·15. The second case with an oil filled anterior chamber had an open iridectomy. The mechanism of aqueous flow through the iridectomy did not function properly because of a large choroidal effusion in the lower quadrants, by which means the aqueous was probably diffusing from the eye instead of by the chamber angle.

At the end of the follow-up period the 6 o'clock iridectomy was closed in five eyes. In one case, as mentioned above, oil was in the anterior chamber. In the remaining four cases, however, no oil was present in the anterior chamber.

In the early postoperative period six iridectomies were closed owing to fibrin or a blood clot. In five of these cases the iridectomy opened spontaneously in two to eight weeks and in one case the iridectomy was reopened with YAG laser, whereupon the oil disappeared from the anterior chamber. In five cases an increase in intraocular pressure to 32 mmHg was noted during the follow-up. All cases could be regulated medically to pressures lower than 21 mmHg. Two patients had a slight band-shaped keratopathy without oil in the anterior chamber. No other silicone oil related corneal opacities were registered.

The Nagoya material contained 27 patients (27 eyes). The mean observation time was 7·0 months, ranging from 3 to 13 months. Of 27 cases 25 had an anterior chamber free of silicone oil. In four cases the iridectomy closed. Two cases had rubeosis iridis, which could explain excessive fibrin clotting, and in the two other cases the iridectomy had been too small.

At the end of the observation period silicone oil was present in the anterior chamber of two of the Nagoya cases: one being a patient with rubeosis iridis and one more case with open iridectomy without further particulars.

Intraocular pressure was elevated over 21 mmHg in four cases, but was regulated within normal limits medically. A slight band-shaped keratopathy was noted in four cases.

COMPARISON WITH CASES FROM PREIRIDECTOMY ERA

To substantiate our impression that a 6 o'clock iridectomy can prevent complications in the silicone oil filled intracapsular aphakic eye we have reviewed all the charts of vitrectomy patients in whom silicone oil was utilised during the last half year preceding the introduction of the 6 o'clock iridectomy. The period thus studied was July through December 1983. We selected all consecutive intracapsular aphakic cases that had an intact or almost intact iris diaphragm and had sufficient follow-up.

Thus, from the Rotterdam material we reviewed 16 cases. The findings are summarised in Table 2. In only five cases did the cornea remain clear. In the other 11 cases either a band-shaped keratopathy or vascularisation and stromal swelling slowly developed as a result of presence of silicone oil in the anterior chamber, mostly in permanent contact with the corneal endothelium.

Of those having a clear cornea, one patient had an anterior chamber full of vitreous protecting the cornea from entrance of the silicone oil. One diabetic patient had a thin membrane in the pupil resulting in a seclusio pupillae on the anterior silicone oil bubble's face. So only three patients were found to have a clear cornea without silicone oil in the anterior chamber without any additional circumstances that supported the retropupillary position of the oil bubble.

Of those 11 cases that developed keratopathy four received a corneal transplant within our follow-up period (up to January 1986). In two cases a secondary 6 o'clock iridectomy was performed and resulted in disappearance of oil from the anterior chamber. The other patients underwent several abrasions and disodium-EDTA treatment to remove the band-shaped keratopathy before the oil could be removed from the eye. In two cases no treatment for the corneal opacification was undertaken because of the bad prognosis of the PVR process within the eye, which did not warrant penetrating keratoplasty.

Discussion

The effect of successful application of silicone oil in the management of retinal detachment in the aphakic eye has until now been seriously hampered by corneal opacification and secondary pressure rises. Permanent contact of silicone oil with endothelium of the cornea is thought to be the cause of these two major complications of intraocular silicone oil. The results of the use of a 6 o'clock iridectomy are clearly demonstrated by the material presented. In the group of patients with an iridectomy at 6 o'clock (62 cases) only 10% of patients developed corneal opacification, and in none of these was a corneal graft needed. In the smaller group (16 cases) that is presented for comparison, which did not have a 6 o'clock iridectomy, the majority of cases (69%) had corneal trouble, either band-shaped keratopathy or corneal decompensation. From these results the advantage of a 6 o'clock iridectomy is obvious.

Table 2 *The cornea and silicone oil: results without 6 o'clock iridectomy in intracapsular aphakic silicone oil surgery*

Number of cases	16
Clear cornea:	5
vitreous in anterior chamber	1
pupillary seclusion	1
Keratopathy:	11
Na-EDTA treated	3
keratoplasty performed	4
secondary iridectomy	2
'accepted'	2

The mechanism by which a 6 o'clock iridectomy prevents silicone oil from entering the anterior chamber is explained as follows. By cohesive forces the silicone oil bubble tends to take on a smooth spherical form within the aqueous filled posterior segment of the vitrectomised aphakic eye. Silicone oil will not enter the anterior chamber as long as it does not create a pupillary block (Fig. 1). With an existing pupillary block the aqueous will accumulate behind the iris diaphragm at the lowest part of the posterior segment. During waking hours this is at the 6 o'clock position behind the iris. Pressure building up by aqueous production forces silicone oil through the pupil and results in an oil filled anterior chamber. An iridectomy at the 6 o'clock position prevents a pupillary block and ensures passage of aqueous towards the chamber angle (Fig. 2). An iridectomy at the 12 o'clock position is less likely to solve the problem because the silicone oil bubble is directly behind the iris and is floating against the diaphragm in the upper part of the eye.

The fact that in a few of our cases no oil was present in the anterior chamber while the iridectomy appeared to be closed is explained as follows. When

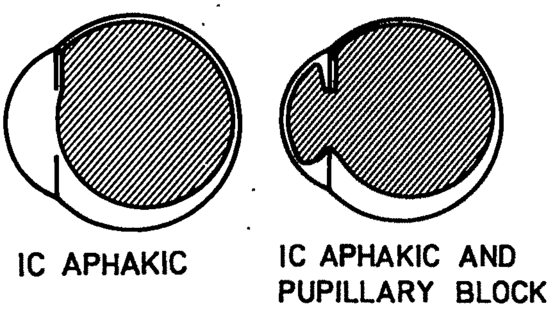
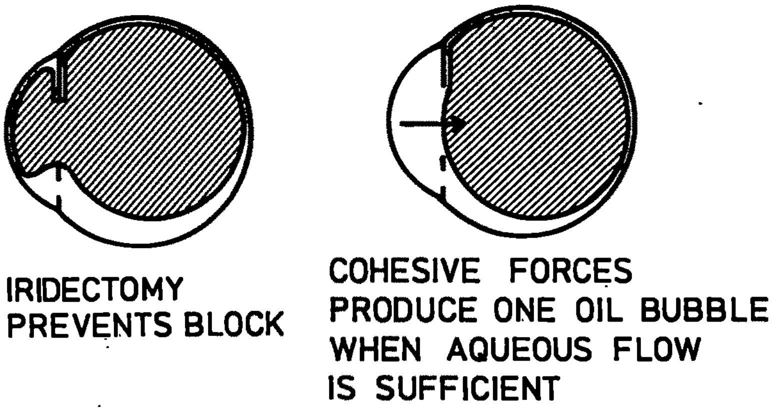


Fig. 1 Left: *silicone oil fills the posterior segment, aqueous passage towards the anterior chamber is patent.* Right: *a slightly larger quantity of oil causes pupillary block, and silicone oil is forced into the anterior chamber. IC= intracapsular.*

Fig. 2 Left: *an iridectomy at the 6 o'clock position allows aqueous flow towards the anterior chamber.* Right: *the oil bubble retracts towards spherical shape as soon as the pupillary block is broken or prevented.*


IRIDECTOMY PREVENTS BLOCK
COHESIVE FORCES PRODUCE ONE OIL BUBBLE WHEN AQUEOUS FLOW IS SUFFICIENT

the posterior segment is not filled completely with silicone oil, the oil bubble is not large enough to cause a complete pupillary block. The lower part of the diaphragm is free of contact with the silicone oil, and aqueous from under the bubble can move into the anterior chamber (Fig. 1, left diagram).

The 6 o'clock iridectomy described here was performed as a primary procedure. However, the iridectomy can be made as a secondary intervention.

Failure of a 6 o'clock iridectomy to achieve an anterior chamber free of silicone oil may have three causes. Either the iridectomy had been too small or the production of aqueous humour had been too low to circulate sufficiently into the anterior chamber. Some eyes with complicated retinal detachment which had multiple surgery, including encircling procedures and cryocoagulation, have a low aqueous turnover rate. The presence of silicone oil, pressing against the ciliary body processes may further decrease aqueous production.

A third cause for the presence of silicone oil in the anterior chamber while the 6 o'clock iridectomy is open is the occurrence of a traction detachment that decreases the volume of the vitreous cavity. Appearance of silicone oil in an anterior chamber that previously was free from oil should alert the surgeon to the possibility of a recurrence of a traction detachment.

An iridectomy at the 6 o'clock position as a routine addition to silicone oil surgery in the aphakic eye has drastically prevented serious anterior chamber complications in our group of patients.

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Microcornea associated with retinopathy of prematurity

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SUMMARY Eight children with retinopathy of prematurity (ROP) in whom the corneal diameters were abnormally small in one or both eyes are reported. The mechanisms for microcornea in ROP are discussed. The differential diagnosis of microphthalmos is briefly considered.

Anterior segment abnormalities are known to occur in association with retinopathy of prematurity (ROP). Recently attention has been directed mainly to anomalies of corneal curvature, and Hittner and coworkers[1] reported abnormally steep keratometry readings associated with shallowing of the anterior chamber. Microphthalmos was reported in the early ROP literature,[2-5] later confirmed by ocular ultrasonography,[6 7] and was considered an accompaniment of advanced cicatricial disease. Since then this aspect of ROP has received little attention.

We present here the cases of eight infants with ROP who also had reduced corneal diameters. In seven of the eight serial measurements were obtained over a minimum period of 15 months. We will discuss this association, consider the possible mechanisms involved in its production, and indicate that in contrast to earlier studies microcornea is not necessarily a sign of advanced cicatricial ROP.

Patients and methods

Eight infants with ROP and reduced corneal diameters have been studied. With the exception of infant 2 all were first examined as part of a routine screening for ROP in one of five neonatal units in Derby, Nottingham, and Leicester. All examinations were performed by ARF using indirect ophthalmoscopy and scleral indentation. Observation for ROP began in the third week of life and continued weekly, clinical condition permitting, until the infant's discharge from hospital and thereafter as needed. Acute ROP was graded according to the new International Classification[8] and the cicatricial changes according to Reese *et al.*[9] Infants who received cryoretinal treatment for acute ROP were excluded from this study. Measurements of horizontal corneal diameter were made with a hand held calliper and rule when infants were on the neonatal unit, or with a ruler after this time. Ocular ultrasound was not performed.

Results

Eight infants, four of each sex, are presented. Gestational ages ranged from between 25·0 and 31·0 weeks and birth weights from 780 to 1360 g. The major systemic problems encountered in the neonatal period are shown in Table 1. All had stormy neonatal periods and all received supplemental oxygen.

The ocular details are listed in Table 2. They

Table 1 *Details of patients*

Case	*Sex*	*Birth weight (g)/ gestation (weeks)*	*Neonatal problems*
1	F	860 g/27·0	RDS, PDA, hypothermia anaemia
2	F	1120 g/28·0	RDS, anaemia
3	M	1340 g/29·0	RDS, PDA, pneumothorax, IVH
4	M	1360 g/29·0	RDS, IVH, pul. haem., ex. transf.
5	F	980 g/28·0	RDS, PDA, pneumothorax, pneumonia, anaemia, CCF
6	M	1300 g/31·0	RDS, PDA, pneumothorax, IVH, DIC, septicaemia
7	M	780 g/25·0	RDS, PDA, pneumonia IVH, septicaemia, anaemia
8	F	780 g/25·0	RDS, PDA, pneumothorax pneumonia

RDS= Respiratory distress syndrome. PDA=Patent ductus arteriosus. IVH=Intraventricular haemorrhage. DIC= Disseminated intravascular coagilopathy. Ex. Transf.=Exchange transfusion. Pul. haem=Pulmonary haemorrhage.
Cases 7 and 8 are twins.

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Table 2 *Ocular details*

Case	*Acute ROP*		*Cicatricial ROP*		*Refractive Error*		*Corneal diameter (mm)*	
	R	*L*	*R*	*L*	*R*	*L*	*R*	*L*
1	III+	III+	V	I	NA	−13·5	9·5	11·0
2	Not examined		III	IV	$\frac{-0{\cdot}5}{-1{\cdot}0}$ at 90	NA	11·0	9·5
3	III+	IV	I	IV	$\frac{-11{\cdot}0}{-2{\cdot}0}$ at 100	+2·0DS	11·0	9·5
4	IV	IV	V	V	NA	NA	10·0	10·0
5	III	II	I	0	$\frac{-12{\cdot}0}{-1{\cdot}0}$ at 180	Plano	10·0	11·0
6	III+	III+	III	II	Plano	$\frac{-7{\cdot}0}{-1{\cdot}50}$ at 180	10·0	11·0
7	III+	III+	III	I	−5·0	−6·0	10·0	10·0
8	III+	III+	I	I	−7·0	−9·0	10·5	11·0

NA = Retinoscopy impossible owing to retrolental opacity. Values for refractive errors and corneal diameters are from the most recent follow-up.

include the maximum grades of acute and cicatricial ROP reached, the refractive status, and the horizontal corneal diameters at the most recent outpatient visit.

Measurements of corneal diameter began at 36 weeks postmenstrual age (cases 7 and 8), and corrected ages of 1 month (case 3), 2 months (cases 1 and 4), and 3½ months (case 6). For infants 2 and 5 measurements were not made until ages 2½ and 3½ years respectively. Except for case 2 all infants had serial assessments over a minimum period of 15 months, on three (cases 1,4,5), four (case 6), five (case 3), and seven occasions (cases 7,8). Except for infants 7 and 8 corneal diameters did not alter between the first and most recent readings. Infants 7 and 8 were twins born at 25 weeks gestation. Both were extremely ill and developed grade 3-plus acute ROP. One month before term the corneal measurements were 9·0 mm in each eye of both infants. At term these were 9·5 mm in all four eyes, at 3 months corrected age 9·5 mm in each eye of one infant and 10·0 mm in the twin. By one year the diameters in infant 7 were, right 10·0 mm and left 10·0 mm, and for the twin (case 8) 10·5 mm in the right eye and 11·0 mm in the left.

In two infants (cases 4 and 7) microcornea was bilateral, while in the other six it was unilateral. Microcornea involved the eye more severely affected by cicatricial ROP in five, while in the remaining infant there was no significant difference in the retinal appearance of the two eyes.

Discussion

The eight infants presented herein all had microcornea in association with cicatricial ROP. In six the condition was unilateral and in two bilateral. In two infants corneal diameters were not measured until 3½ years of age, by which time the ROP process had reached a stable cicatricial stage. For the remaining six infants, however, measurements began from 39·0 to 48·0 weeks postmenstrual age, at a time when ROP was either still in the acute phase or just entering the cicatricial phase. For the six infants with adequate data across both acute and cicatricial phases (cases 1,3,4,6,7,8) no reduction of corneal diameter was detected after the first reading, and in these infants microcornea is likely to be due to a failure of growth and not to secondary globe shrinkage. In five of the six unilateral cases the smaller cornea was in the eye containing the more advanced cicatricial ROP, though in one infant (case 8), while there was no significant difference in ROP between the two eyes, yet a minor degree of microcornea (0·5 mm) of one eye was present.

Accurate assessment of corneal diameter in infancy is difficult. Our readings are not suitable for the study of corneal growth, but they do indicate a trend and can be used to detect interocular differences. At birth (full term) the horizontal corneal diameter (HCD) is 10·0 mm, reaching adult values some time in the first year.[10,11] The normal adult 'white to white' HCD is 11·64 (SD 0·49) mm.[12]

Terry,[2] Cohen *et al.*[5] and King,[3] in the early literature on ROP, noted microphthalmos as a feature of severe cicatricial retrolental fibroplasia. King implied that the retrolental membrane inhibited ocular growth, while Owens discussing that paper stated: 'in none of the eyes in which retrolental fibroplasia developed was the cornea smaller before the onset of the disease in the retina'.[3] No corneal measurements were contained in these articles, though the authors' observations that the cornea is normal initially and fails to grow is also our impression and confirmed by cases 7 and 8. We do not consider a retrolental membrane to be the sole cause of delayed ocular growth, as in only four eyes of three of our infants did a membrane develop. Furthermore in our infants ocular growth was abnormal before this late stage. In all probability this is not specific to ROP but a consequence of severe ocular disease, particularly if involving the anterior section of the eye, during this period of ocular growth. We conclude therefore that growth may be adversely affected during severe acute stages of ROP and is not necessarily a sign of advanced cicatricial disease. We also found, with the exception of case 8, where the acute ROP and cicatricial ROP were symmetrical, the microcornea present in the eye with the more advanced disease. Machemer[13] has recently discussed retinal tissue contraction in advanced ROP, and it would not be surprising for late shrinkage of the globe to occur sometimes, though this was not a feature seen in our study.

Since ocular ultrasound was not possible in this study, it is not known whether microcornea is associated with microphthalmos in our patients. Microphthalmos in ROP has been confirmed by A scan ultrasound,[6 7] but axial length does not necessarily correlate with the degree of myopia.[14] Hittner *et al.*[1] failed to correlate myopia with increased corneal curvature, though all their patients had received surgical treatment which itself could have adversely affected ocular growth. In association with microcornea we found myopia in four eyes of three infants, no refractive error in two eyes of two infants, while in three infants a retrolental mass precluded retinoscopy. Anomalies of corneal curvature may be a factor for myopia in some cases of ROP.

Microcornea has been recognised as a feature of advanced ROP since the first descriptions of this condition, but the pattern of ROP has changed over the past 30 years, and we have shown this also occurs with mild cicatricial ROP, though the frequency of this association is unknown. Cases 1, 6, and 7 also illustrate that bilateral acute symmetrical ROP can lead to asymmetrical cicatricial ROP.

Microcornea/microphthalmos is a feature of many ocular malformations, some of which have important genetic implications. This preliminary study indicates that the presence of microcornea or microphthalmos does not eliminate ROP as a differential diagnosis in infants with this abnormality or leucocoria—all the more so since on occasion ROP can occur in full term infants not exposed to supplementary oxygen.[15]

We thank Mrs Jill Wood for typing the manuscript.

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Congenital horizontal tarsal kink: a simple surgical correction

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SUMMARY A case is reported in which a simple anterior lamellar repositioning procedure was used successfully to repair an upper lid entropion associated with a horizontal tarsal kink. This obviates the need for the more complex and destructive procedures which have previously been described for the treatment of this condition.

Congenital horizontal tarsal kink is a rare form of upper lid entropion. It presents in infancy with trichiasis and secondary blepharospasm, photophobia, and keratitis. It is due to a horizontal kink in the tarsal plate, causing rotation of the marginal 2–3 mm of tarsus through more than 90° towards the globe. The skin crease is absent, and the condition may be unilateral or bilateral. Associated systemic abnormalities affecting the cardiovascular and central nervous system have been reported, as in other types of primary upper lid entropion.[1] The previously reported surgical management of these cases has involved relatively complex lid splitting procedures or excision of part of the tarsus.

We present a case of unilateral congenital horizontal tarsal kink, and describe a simple, effective surgical procedure for its correction.

Case report

A 6-month-old Caucasian male child was referred for entropion repair. He had been found to have a sticky right eye soon after birth and was treated with several topical antibiotics.

On examination he was found to have a right upper lid entropion with trichiasis and lid retraction. There was no skin crease. No other ocular abnormality was detected, and the left eyelids were normal (Fig. 1).

The child was born at term after an uncomplicated pregnancy and delivery, and there was no ocular family history of note. His neurological development was within normal limits, and no other systemic abnormalities could be found.

At operation he was found to have a horizontal tarsal kink of the right upper lid, which could not readily be reduced and was situated 2–3 mm from the lid margin (Fig. 2). The tarsal kink was corrected by an anterior lamellar repositioning procedure, in which a skin crease incision was made and the anterior lamella of skin and orbicularis undermined to the lash roots. 6/0 Polyglycolic acid sutures were passed through the skin just above the lashes and into the tarsal plate at a higher level, this level being adjusted to provide the desired lid eversion. Levator and Müller's muscles were disinserted from the tarsus to overcome the associated lid retraction and reattached to the anterior lamella by the skin crease sutures to increase the lash eversion[2] (Fig. 3).

Postoperatively the child recovered well, and eight months after surgery the lid remained at a good level, with the lashes well everted (Fig. 4).

Discussion

Upper lid entropion is uncommon and almost always due to cicatricial shortening of the tarsoconjunctiva. Surgical repair relies on eversion of the lid margin, with lengthening of the posterior lamella of the lid as required.[2]

Horizontal tarsal kink is a very rare form of upper

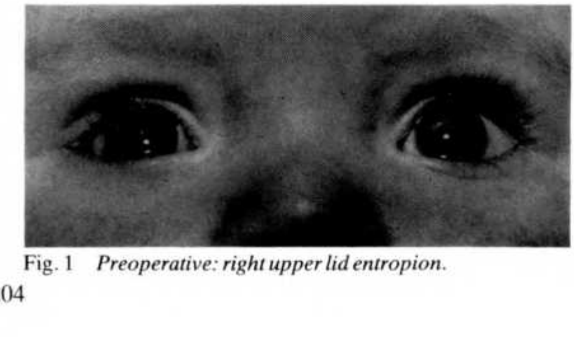

Fig. 1 *Preoperative: right upper lid entropion.*

Correspondence to N C Price, FRCS.

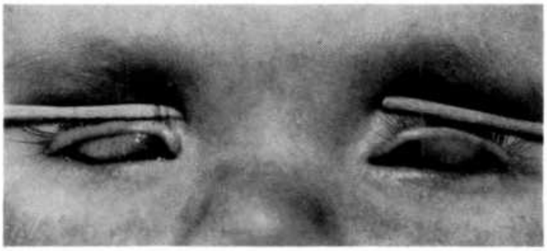

Fig. 2 *Everted right upper lid to show horizontal tarsal kink.*

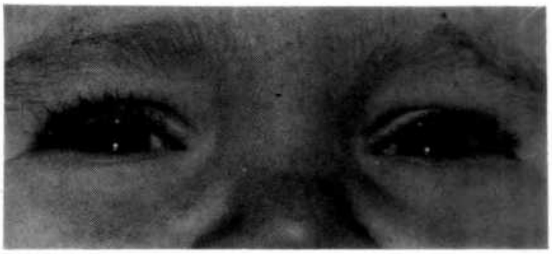

Fig. 4 *Eight months after surgery.*

lid entropion. Hiles and Wilder[1] included only two cases in their report of 14 patients with congenital upper lid entropion (one previously reported by Callahan[3]), and four other cases have been reported so far.[4-7]

In five cases presentation was within the first few weeks of life, with inflamed and sticky eyes and blepharospasm. Five patients are said to have had keratitis or frank corneal ulceration at the time of presentation. Three patients had bilateral tarsal kinking, and four, including ours, had abnormalities restricted to the right lid.

The aetiology of the kink is unknown. It has been suggested that overaction or malpositioning of the marginal fibres of the orbicularis muscle may cause tarsal infolding in utero, and the attachments of the aponeurosis to form the skin crease may be defective. The alternative is a primary lesion in the tarsus itself.

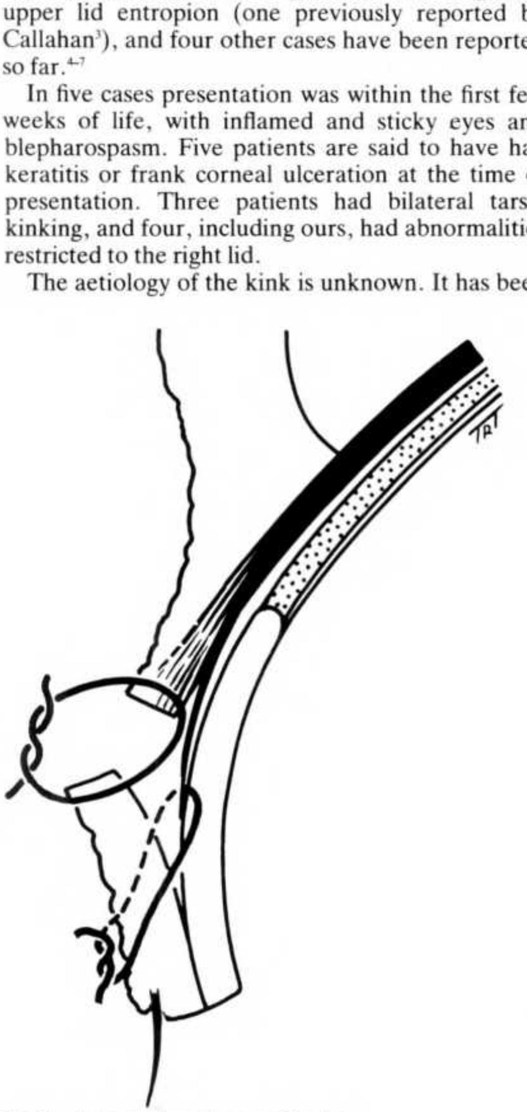

Fig. 3 *Anterior lamellar repositioning.*

Hiles and Wilder[1] drew attention to the association of congenital upper lid entropion with other systemic abnormalities, affecting the cardiovascular and skeletal systems and the mental development of six of their 14 patients. More recently Zak[8] found multiple cardiovascular, musculoskeletal, and central nervous system abnormalities in a child with congenital primary upper lid entropion. There is no mention of associated abnormalities in the 'tarsal kink' papers reviewed, and our child is developmentally normal. However, the incidence of associated developmental abnormalities in children with congenital primary upper lid entropion is such that all children with upper lid entropion should be carefully assessed by a paediatrician, with particular reference to the skeletal, cardiovascular, and nervous systems.

The surgical management of the horizontal tarsal kink has varied in all reported cases. Callahan[3] and Quickert *et al.*[6] advocated resection of the kink and everting sutures. Biglan and Buerger[4] and Crawford and Main[5] were concerned that resection of part of the tarsus may cause lid shortening, and treated their patients by horizontal tarsal splitting and everting sutures. McCarthey[7] carried out a complex lamellar tarsoplasty.

All these procedures were described as successful in correcting the entropion, but all were destructive to the tarsus, either by excision of the part of the tarsal plate or by full-thickness incision through it. Most authors have considered that a simple 'skin and muscle' operation would not provide enough everting strength to hold the tarsus straight, though Hiles and Wilder[1] have successfully treated one case by such an operation. Kettesy[9] reported a case of tarsal folding (but not a true horizontal tarsal kink) which was treated by splinting the lid in a normal position with mattress sutures and a bolster of gauze.

In our case, five 6/0 polyglycolic sutures were passed through the skin above the lash roots and into the upper part of the tarsus before exiting through the skin again. The eversion produced by such sutures lasts at least two months and allows scarring of the anterior lamella of the lid, which holds the tarsus everted. The eversion is further increased dynamically by attaching the upper lid retractors to the skin edges. The tarsus and meibomian glands are left intact.

In our view horizontal tarsal kink syndrome can be adequately repaired by a simple anterior lamellar reposition without resort to complex and more destructive lid procedures. This supports the view that the primary lesion is in the orbicularis muscle or in the formation of a skin crease and not in the tarsus, since altering the position of the orbicularis muscle and creating a skin crease can cure the condition.

We thank Mr B J Power for kindly referring this patient and agreeing to this publication.

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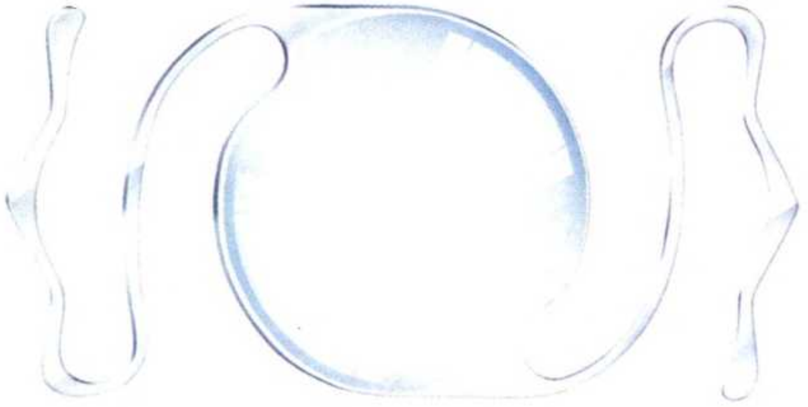

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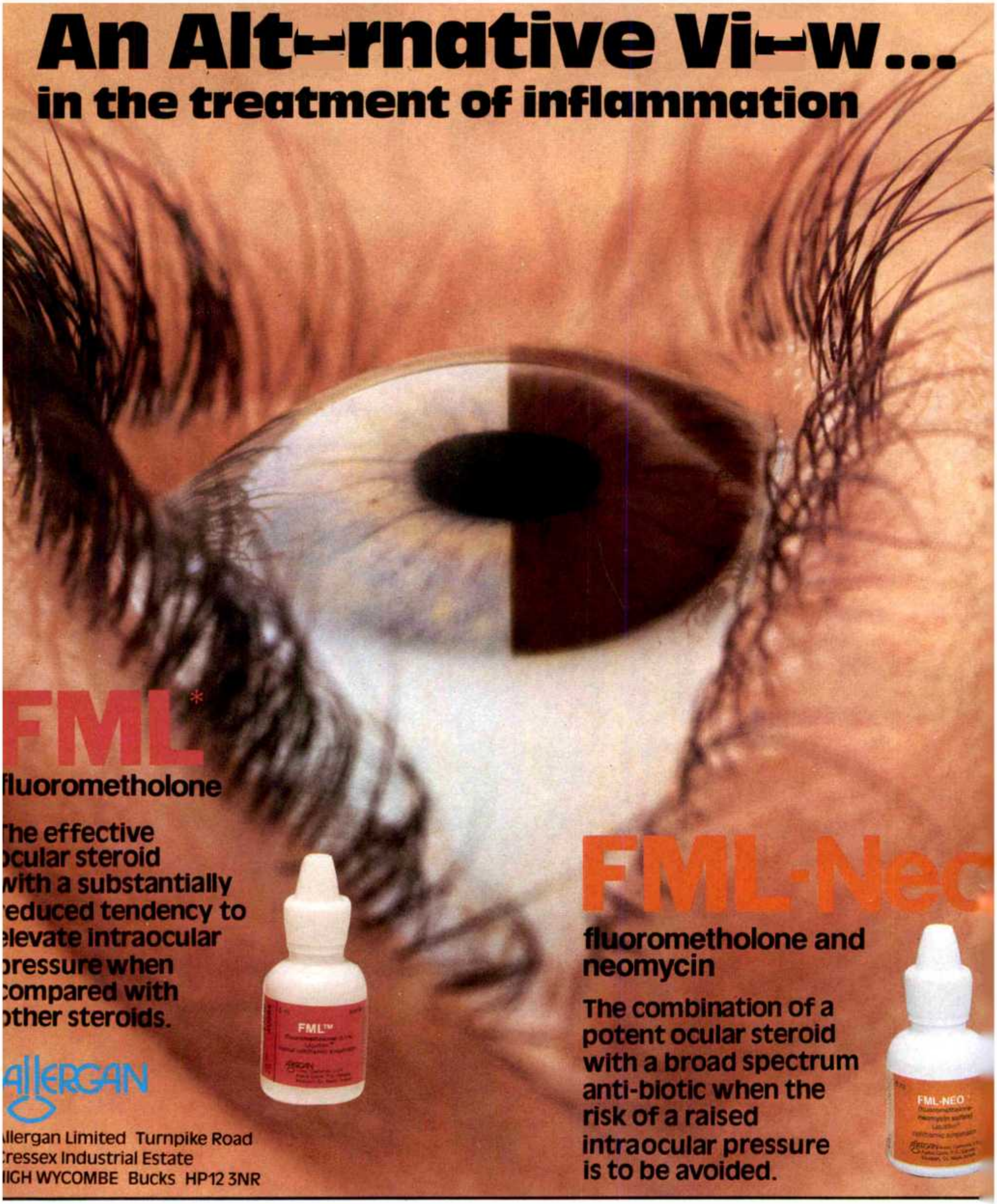

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During the initial 24 to 48 hours, the dosage may be safely increased to one drop every hour. Care should be taken not to disc
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British Journal of Ophthalmology, 1987, **71**, 207–211

Corneal thickness, astigmatism, and atopy

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SUMMARY Keratometry and regional pachometry were performed on atopic patients with no history or signs of atopic keratoconjunctivitis. In a series of 80 eyes there was a skewed distribution towards thinner corneas ($p<0.01$) and a preponderance of against-the-rule astigmatism. The maternal age at birth of this group of patients was higher than that in the general population. These findings are discussed in the context of the known association of atopy with keratoconus.

The term 'atopy' was used by Coca and Cooke[1] to indicate a hypersensitivity response to common allergens which was subsequently found to be mediated by a specific class of immunoglobulin IgE.[2] Atopy is thus defined as the capacity to produce IgE (reaginic) antibodies to various common environmental allergens.[3] Eczema, asthma, and hay-fever are the principal conditions within the group, but there is considerable variety and range of severity of manifestations among affected individuals.

The premise for this study is based on four observations. First, there is a high prevalence of atopy among patients with keratoconus[4-6]; secondly, irregular corneal astigmatism is associated with keratoconus[7,8]; thirdly, the slit-lamp signs, retinoscopy, and keratometry findings in keratoconus are preceded by corneal thinning[9]; fourthly, Kornerup and Lodin as part of their investigation of atopic cataract recorded a high prevalence of irregular corneal astigmatism.[5]

The aim of this study was to compare the thickness and curvature of the cornea in atopic patients without ocular disease with those in the normal population.

Material and methods

SELECTION OF PATIENTS

Subjects were selected from the respondents to an invitation to participate in a study of the cornea in atopy which was placed in the *Eczema Journal*, a quarterly publication of the Eczema Association, and from referrals from a dermatologist. Subjects with a history or signs of ocular disease, or who had ever worn contact lenses, were excluded. Atopy was diagnosed by a consultant physician. Eighty eyes were examined.

INVESTIGATIONS

A questionnaire was completed which detailed the ocular and atopic history of each subject and his/her immediate family. In view of the reported higher incidence of keratoconus among children of older mothers[9] the maternal age at birth was recorded. After testing Snellen visual acuity, refraction, and a slit-lamp examination, corneal curvatures were measured with the American optical keratometer.

A modification of the Haag-Streit pachometer first suggested by Donaldson[10] and modified by Mandell and Polse[11] was used for the measurement of corneal thickness centrally and at four midperipheral points. The conventional pachometer requires the subject to view the incident light beam with the microscope set obliquely (at 45°). Corneal thickness is thus measured along the visual axis only and does not permit an exact comparison between eyes, particularly if there is a large angle between the visual and geometric axes.[12] In order to reduce these errors measurements were taken at the geometric centre of the cornea.

To measure peripheral corneal thickness at the same distance from the optical centre in every eye the following system was used. The microscope is perpendicular to the cornea and the incident light beam strikes obliquely. For measurements on the geometric axis the subject fixates between two green light emitting diodes (LEDs) mounted in an acrylic plate (Fig. 1), and the microscope adjusted so that their corneal reflections are symmetrically disposed in the eyepiece. The four red LEDs, each of which subtends an angle of 14° to the cornea, serve as

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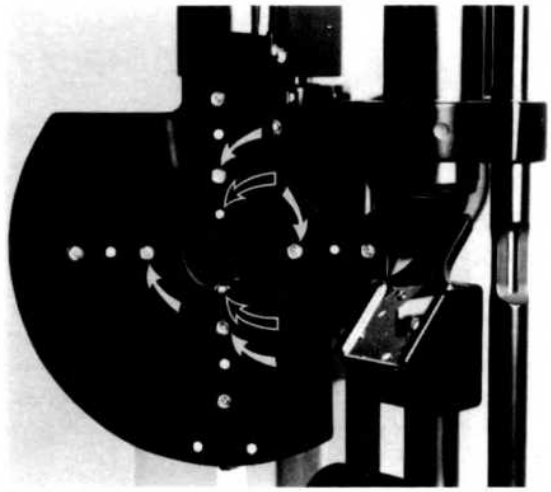

Fig. 1 *Light emitting diodes (LEDs) mounted in an acrylic plate and fixed to the housing of a Haag-Streit 900 slit-lamp. Open arrows=green LED; closed arrows=red LED which subtend an angle 14° to the geometric axis.*

fixation points for midperipheral measurements of corneal thickness. This technique allows successive measurements of the same site on the cornea. A potentiometer is coupled to the measuring shaft of the basic instrument to improve observer accuracy and to provide a digital read-out. Three readings were taken at each position and the mean figure taken.

The youngest patient was 12 years old, and, although attempts were made to measure younger patients, fixation was unsatisfactory. Those with poor fixation due to presbyopia were also excluded. One case of keratoconus was diagnosed from the respondents and excluded from the study.

Results

There were 20 male and 20 female subjects. Their atopic symptoms are shown in Table 1. The frequency distribution of maternal age at birth in the general population in 1960, which corresponds to the median birth year of the subject group, is given in Table 2. Paternal age was not recorded by the

Table 1 *Additional atopic history*

Asthma	62·5%
Hay-fever	62·5%
Food allergies	7·5%

Table 2 *Frequency distribution: maternal age at birth: general population 1960*

	<20	*20–24*	*25–29*	*30–34*	*35–39*	*40–44*	*45–49*	*Total*
No.	46 067	229 064	233 579	143 475	77 261	17 736	1315	748 498
%	6·15	30·50	31·21	19·17	10·32	2·37	0·18	100

Source: *Registrar General's Statistical Review*. London: Office of Population and Census Surveys, 1960.

Table 3 *Frequency distribution: paternal age at birth: general population 1961*

	<20	*20–24*	*25–29*	*30–34*	*35–39*	*40–44*	*<45*	*Total*
No.	621 000	305 000	234 900	151 000	77 000	35 000	16 300	1 480 200
%	43·10	21·18	16·30	10·48	5·30	2·43	1·13	100

Source: *Registrar General's Statistical Review*. London: Office of Population and Census Surveys, 1961.

Table 4 *Frequency distribution: maternal age at birth: subjects*

	<20	*20–24*	*25–29*	*30–34*	*35–39*	*40–44*	*45–49*	*Total*
No.	0	6	10	15	6	2	0	39
%	0	15·38	25·64	38·45	15·38	5·12	0	100

One subject adopted—maternal age not known.

Table 5 *Frequency distribution: paternal age at birth: subjects*

	<20	*20–24*	*25–29*	*30–34*	*35–39*	*40–44*	*>45*	*Total*
No.	0	3	10	12	7	3	3	38
%	0	7·89	26·31	31·57	18·42	7·89	7·89	100

Paternal ages not known in two cases.

Table 6 *Frequency distribution of central corneal thickness (mm) in atopic subjects*

CCT	0·47	0·48	0·49	0·50	0·51	0·52	0·53	0·54	>0·55
No.	2	3	7	14	11	13	18	10	Nil

CCT=central corneal thickness.
Number of eyes=78.
Mean central corneal thickness=0·514, SD 0·025 mm.

Table 7 *Central corneal thickness in normal eyes*

Author	*Corneal thickness (mm±SD)*	*No. of eyes*	*Year*
Donaldson[10]	0·522±0·041	268	1966
Martola and Baum[18]	0·523±0·041	268	1966
Lowe[19]	0·517±0·034	157	1969
Kruse Hansen[12]	0·520±0·018	76 (R)	1971
Kruse Hansen[12]	0·524±0·02	74 (L)	1971

Number of eyes=784.
Mean central corneal thickness=0·521 mm.

Registrar General until 1961 (Table 3), which precludes strict comparative analysis. The frequency distribution of maternal and paternal age at birth of the subjects is shown in Tables 4 and 5. Eighty eyes had corneal thickness measurements taken at five points. The measurements were taken at the geometric centre of the cornea and at four points corresponding to a rotation of the eye by 14°. Results were discarded from one patient as being unreliable owing to poor fixation.

CENTRAL CORNEAL THICKNESS

The frequency distribution for central corneal thickness for the 78 remaining eyes is given in Table 6. The mean value was 0·514 mm. Measurements of central corneal thickness in normal eyes are given in Table 7, with a mean value of 0·521 mm. Kruse Hansen found a difference between right and left eyes which was thought to be due to the technique being susceptible to a different measurement on the two eyes owing to angle kappa.[12]

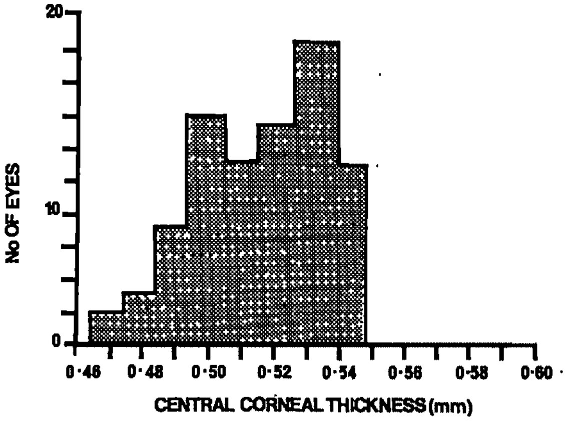

Fig. 2 *Distribution of central corneal thickness in eyes of atopic patients.*

All authors reported that in healthy eyes corneal thickness is Gaussian in distribution.[12]

Plotting the findings for this study indicated that the distribution in the atopic group might not be Gaussian (Fig. 2). The results were therefore submitted to statistical analysis. An appropriate analysis is the χ^2 goodness of fit test, where observed frequencies are compared with expected frequencies for a normal distribution (Table 8).

For eight classes there are 6 degrees of freedom. Critical χ^2 with df 6 at $p=0{\cdot}05$ is 12·59, which is just larger than the result found (12·58). Although at $p=0{\cdot}05$ there is not a statistically significant deviation from a normal distribution, for $p=0{\cdot}10$ $\chi^2=10{\cdot}67$ it is significant. If the sample had been increased to 105 eyes, it might have proved significant at $p=0{\cdot}05$.[13]

MID PERIPHERAL CORNEAL THICKNESS

The results for midperipheral corneal thickness accorded with those of other workers.[14] However, in four eyes the thinnest reading was from one of the midperipheral points rather than the centre. One of these showed slight irregularity of keratometer mires; the other three were regular. Two had a visual acuity of 6/5 and two 6/12.

CORNEAL CURVATURE

Keratometry was performed satisfactorily on 80 eyes. These results were then analysed into four classes: (1) against-the-rule astigmatism; (2) with-the-rule astigmatism; (3) spherical; (4) oblique astigmatism.

Table 8 χ^2 *goodness of fit test for central corneal thickness in atopes*

Range	*Observed*		*Expected*		*(Observed-expected)²*	χ^2
<0·475	2	5	4·633	9·594	$-4{\cdot}594^2/9{\cdot}594$	2·1998
0·475 to 0·485	3		4·691		$-1{\cdot}961^2/4{\cdot}691$	0·7752
0·485 to 0·495	7		7·846		$-0{\cdot}846^2/7{\cdot}846$	0·0912
0·495 to 0·505	14		10·592		$3{\cdot}408^2/10{\cdot}592$	0·0965
0·505 to 0·515	11		12·215		$-1{\cdot}215^2/12{\cdot}215$	0·1209
0·515 to 0·525	13		12·012		$0{\cdot}988^2/12{\cdot}012$	0·0813
0·525 to 0·535	18		10·101		$7{\cdot}899^2/10{\cdot}101$	6·1700
0·535 to 0·545	10		7·254	15·639	$-5{\cdot}639^2/15{\cdot}639$	2·0332
>0·545	0		8·385			
Total						12·5751

Table 9 *Corneal astigmatism in normal eyes*[16]

	Before age 25 (n=1018)	*After age 50 (n=1025)*
Against	24 (2·35%)	118 (11·51%)
With	910 (89·39%)	737 (71·9%)
Spherical	52 (5·10%)	84 (8·19%)
Oblique	32 (3·14%)	86 (8·39%)

Table 10 *Corneal astigmatism: atopic subjects*

Against	=44	55%
With	=11	13·75%
Spherical	=17	21·25%
Oblique	= 8	10·00% %

Mean age=24·28. Standard deviation=10·54. No.=80.

Against-the-rule astigmatism was considered to be present when the flatter corneal meridian lay within 15° of the vertical and with-the-rule when the steeper corneal meridian lay within 15° of the vertical. This is similar to the classification used by Duke-Elder[15] and Borish.[16]

Corneae were classified as spherical when the difference in radii of curvature between the two principal corneal meridians was 0·04 mm or less. The accuracy of measuring the axis of corneal astigmatism decreases as the difference in corneal curvature between the two meridians decreases.

Where the principal corneal meridians lay more than 15° from the vertical or horizontal, the cornea was classified as oblique. Corneal astigmatism in normal persons and the atopic group are given in Tables 9 and 10.

Discussion

The finding of Kornerup and Lodin[5] that there is a higher prevalence of irregular corneal astigmatism was not confirmed, but a significant variation from the normal population was found when the axis of the flatter corneal meridian was observed.

Corneal thickness measurements showed a significant variation from the norm at p=0·1, very nearly significant at the p=0·05, and a larger sample may have confirmed this. The skewedness of the variation was towards thinner corneae, as can be seen from Fig. 2.

Tables 2 and 4 show a higher percentage of older mothers in the subject group compared with the general population born in 1960, which corresponds to the median birth year of the subject group. Paternal age was not recorded by the Registrar General until 1961, and therefore an exact comparison with the subject group is not possible. Furthermore, parental age is recorded only for legitimate births, which comprised 86% of total births in 1961. With this proviso, however, it can be seen from Tables 3 and 5 that there is a high percentage of older fathers in the subject group.

These three findings of against-the-rule astigmatism, corneae thinner than normal, and higher maternal age at birth parallel the findings in patients with early keratoconus.[17] It has long been established that patients with keratoconus have against-the-rule myopic astigmatism at presentation which may progress to irregular astigmatism. However, in this group all but one subject had normal vision either unaided or with spectacles and had none of the additional features of keratoconus.

Furthermore the distribution of corneal thicknesses in the subjects is similar to those with established early keratoconus.[9] Thus, together with the maternal age findings, it could be postulated that the subjects in the study represent a point on the continuum of corneal variation whose extreme presentation is keratoconus.

It is accepted that some subjects were self-selecting in that they responded to an advertisement in the *Eczema Journal* and the resulting sample for study is not necessarily unbiased.

We thank Dr J Leonard and Dr C Roland Payne for referring patients, Mr R J Buckley for helpful criticism, Mr Alan Lacey for the photographs, and Miss C A Smyth and Miss C Dobney for secretarial assistance.

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Comparison of aqueous humour and serum zinc levels in humans

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SUMMARY Zinc concentrations in aqueous humour and serum were determined by means of atomic absorption spectrophotometry in 11 patients with cataract. The zinc content of the aqueous humour was found to be considerably lower than the corresponding serum values. From this finding it is suggested that aqueous humour does not serve as a likely route of delivery of zinc to the cornea.

Recently universal interest in trace elements has stimulated many studies to determine the basic elemental composition of tissues and body fluids. Data on the normal variations of trace element concentrations can be used in determining the pathological significance of alterations found in disease states.

Zinc levels of ocular tissues in man and various other species are well known; their normal variations and pathological concentrations have been elucidated.[1-4] Although the knowledge of zinc metabolism in the cornea is not extensive, it is assumed that this element is delivered to the cornea primarily by three routes: serum, aqueous humour, and tears, as are many other nutrients. Zinc concentrations in serum and tears have been studied, but very little is known about the role of zinc in the aqueous humour. The present study is designed to determine the aqueous humour zinc concentrations in patients with cataract and to correlate these with serum zinc levels in the same individuals.

Materials and methods

Eleven cataract patients undergoing surgery were randomly selected and the zinc concentrations in aqueous humour and serum were determined as outlined below. In each case we obtained medical and dietary histories and carried out a physical examination.

Aqueous humour samples (0·1 to 0·3 ml) were collected with a tuberculin syringe during the initial stage of cataract surgery. Care was taken to ensure that the wound was free of blood to avoid contamination. A sample of blood was also drawn at the time of surgery. Both specimens were placed in metal-free test tubes and capped with paraffin film. The samples were taken to the laboratory for immediate processing. Zinc levels on all samples were determined in the same laboratory with a Perkin-Elmer flame atomic absorption spectrophotometer, model 703, and HGA 400 graphite furnace. The serum samples were diluted 1:4 serum to double dionised water. The aqueous humour samples were not diluted. For standardisation the Perkin-Elmer Atomic Absorption Manual (January 1982) was used. The detection limits for the flame atomic absorption spectrophotometry were 1 ng/ml and for the graphite furnace 1 pg/ml. The reproducibility of the assay was 0·5±2% and ±5% (±%SD) for the flame atomic absorption spectrophotometry and graphite furnace respectively.

Results

The study included 11 patients with senile cataracts, five males and six females. Ages ranged from 50 to 73. All patients denied any significant dietary deficiencies in the past. Medical disorders among the group included hypertension, diabetes mellitus, a past history of tuberculosis, chronic pulmonary fibrosis, and sickle cell trait.

Serum zinc levels ranged from 0·705 to 1·06 μg/ml, average 0·87 μg/ml±0·124 (SD) (Fig. 1). Normal laboratory values for men were 1·2±0·20 μg/ml and for women 0·96±0·13 μg/ml. The average values for

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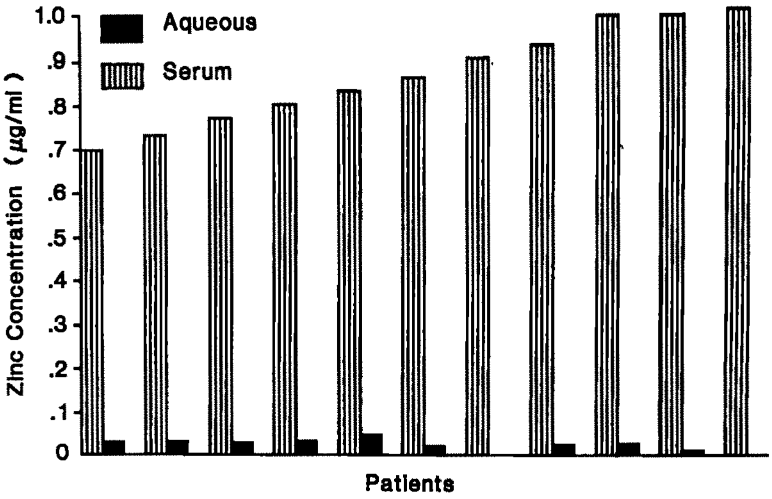

Fig. 1 *Approximate comparison of serum and aqueous humour zinc concentrations.*

our study group were 0·75 µg/ml for men and 0·96 µg/ml for women.

Aqueous zinc levels ranged from 0·0001 µg/ml to 0·021 µg/ml. The average value was 0·0088 µg/ml±0·055 (SD). The average concentration for males was 0·012 µg/ml and for females 0·005 µg/ml. One aqueous sample was too small to be evaluated and one sample was lost in processing.

A Pearson product moment correlation coefficient of serum versus aqueous humour zinc levels was calculated to be −0·27, indicating no significant correlation between the two.

Discussion

Zinc is an essential trace element for human growth and is an integral component of many proteins and metalloenzymes.[5-7] In particular zinc is needed for the maintenance of an intact immune system and for the stabilisation process of nucleic acids, cell membrane, and cellular organelles.[7]

Tauber and Krauss first established the presence of zinc in the eye in 1943.[1] Later it was shown that the concentration of this metal in ocular tissues is unusually high in comparison with the other parts of the body. The zinc concentration of ocular tissues in descending magnitude are the iris, choroid, sclera, vitreous, lens, cornea, and retina.[4] The corneal zinc content has been reported as 19·6, 29·8, 41·0 µg/g in different studies, and, although the details are not well known, this element's role in corneal metabolic functions is well accepted.[4,8,9] Feiler and coworkers have shown that both epithelial and stromal herpes simplex keratitis developed more rapidly in zinc deficient rabbits.[10] The data from our animal experiments indicate that epithelial and stromal corneal wound healing are markedly delayed in zinc deficient rabbits (Lim J, Karcioglu Z A, unpublished data).

Since corneal wound healing is basically similar to wound healing in skin and other mucosal membranes, it is not surprising to observe delayed healing in zinc deficient states. The effects of zinc on wound healing have been studied well in a number of clinical and experimental trials involving skin and other mucosal tissues, and the studies from a variety of species indicate that zinc is essential for normal wound healing.[11,12]

Zinc has an essential role in a wide spectrum of enzyme systems which affect many metabolic processes, including carbohydrate, protein, and nucleic acid syntheses, which are the basic activities required in tissue repair.[6,7] Furthermore, zinc takes part in the stabilisation process of cellular membranes and intracellular organelles. The therapeutic benefit of zinc in wound repair in humans has also been well documented in a number of clinical trials.[12-14] Hubbard and coworkers tested the use of topical zinc application on wound healing in the corneas of zinc deficient rabbits, but were unable to show any beneficial effects.[15] Our studies, on the other hand, performed on zinc deficient experimental animals, clearly indicate a prolonged healing process as measured by the tensile strength of the wound (Lim J, Karcioglu Z A, unpublished data).

Since the role of zinc in the corneal repair process is obvious, it is quite important to determine the route of delivery of this element to cornea. Although our knowledge in this respect is quite limited, it would be reasonable to assume that zinc is delivered to the cornea primarily by three routes: in serum from limbal capillaries, in aqueous humour, and in the tear layer, like other nutrients. Serum zinc in healthy individuals is approximately 1 μg/ml.[7] In our laboratory the normal values for men are 1·2±0·2 μg/ml and for women 0·96±0·13 μg/ml (±SD). In the tear layer the zinc concentration has been determined to be 1·02±0·31 μg/ml in healthy individuals.[16] The zinc concentrations in the aqueous humour, on the other hand, have not been studied well. In one previous study the aqueous humour concentration has been calculated to be 0·359 μg/ml.[17] In another report, the mean value of zinc in aqueous humour was found to be 1·04 μg/ml, but in this study an *x*-ray fluorescein technique was used. The method is old and does not lend itself well to be compared with the previously mentioned report and also with our study.[18]

To the best of our knowledge no comparison of values for aqueous humour and serum has been done previously in simultaneous determinations. The aqueous humour zinc concentrations in our study were extremely small and considerably lower than the corresponding serum values. The average value for the serum zinc concentration was approximately 100 times more than the average value of the aqueous humour zinc. This is not specially surprising, since zinc in serum is bound to proteins, and the total protein level in serum is much higher than the total protein value in the aqueous humour.[19] Aqueous humour in humans has 0·1%–0·2% the concentration of plasma protein.[20] Whatever the reason for the very low zinc levels in aqueous humour, since the average corneal zinc concentration varies between 20 and 40 μg/ml, the aqueous does not appear to be a likely route of delivery of zinc to the cornea.

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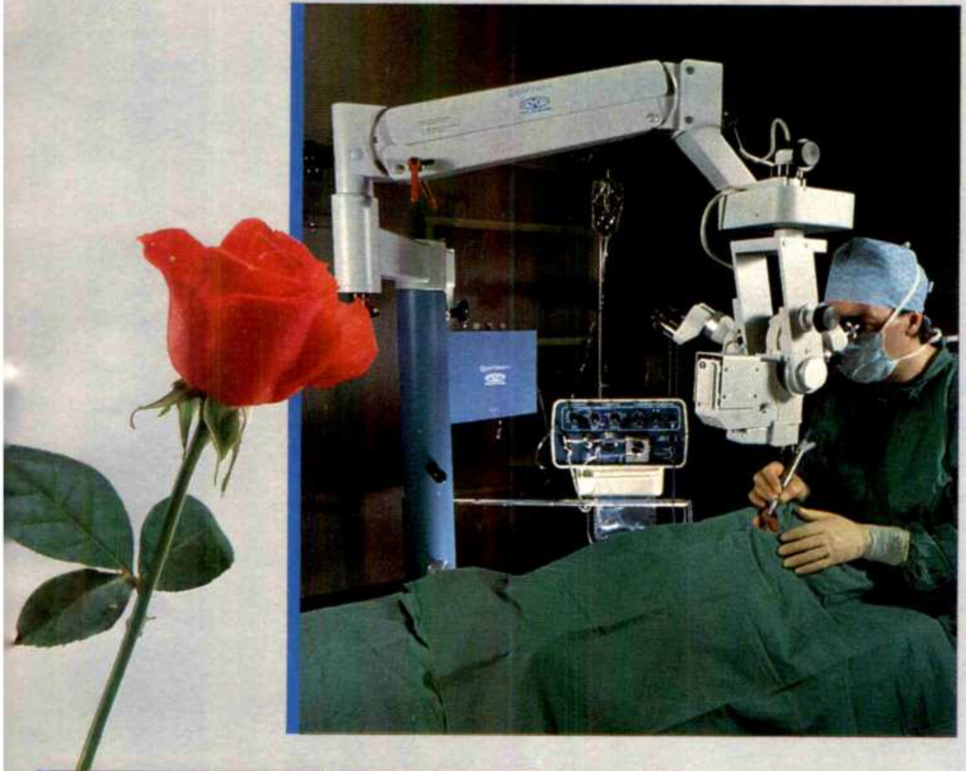

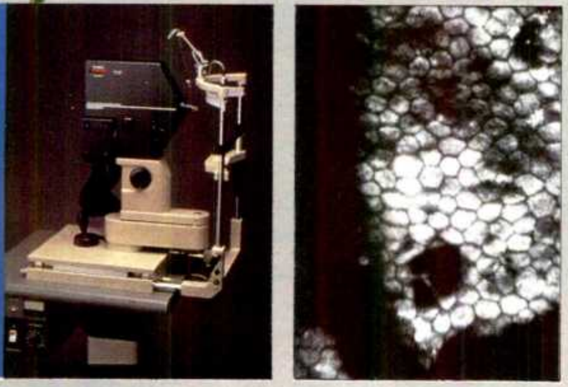

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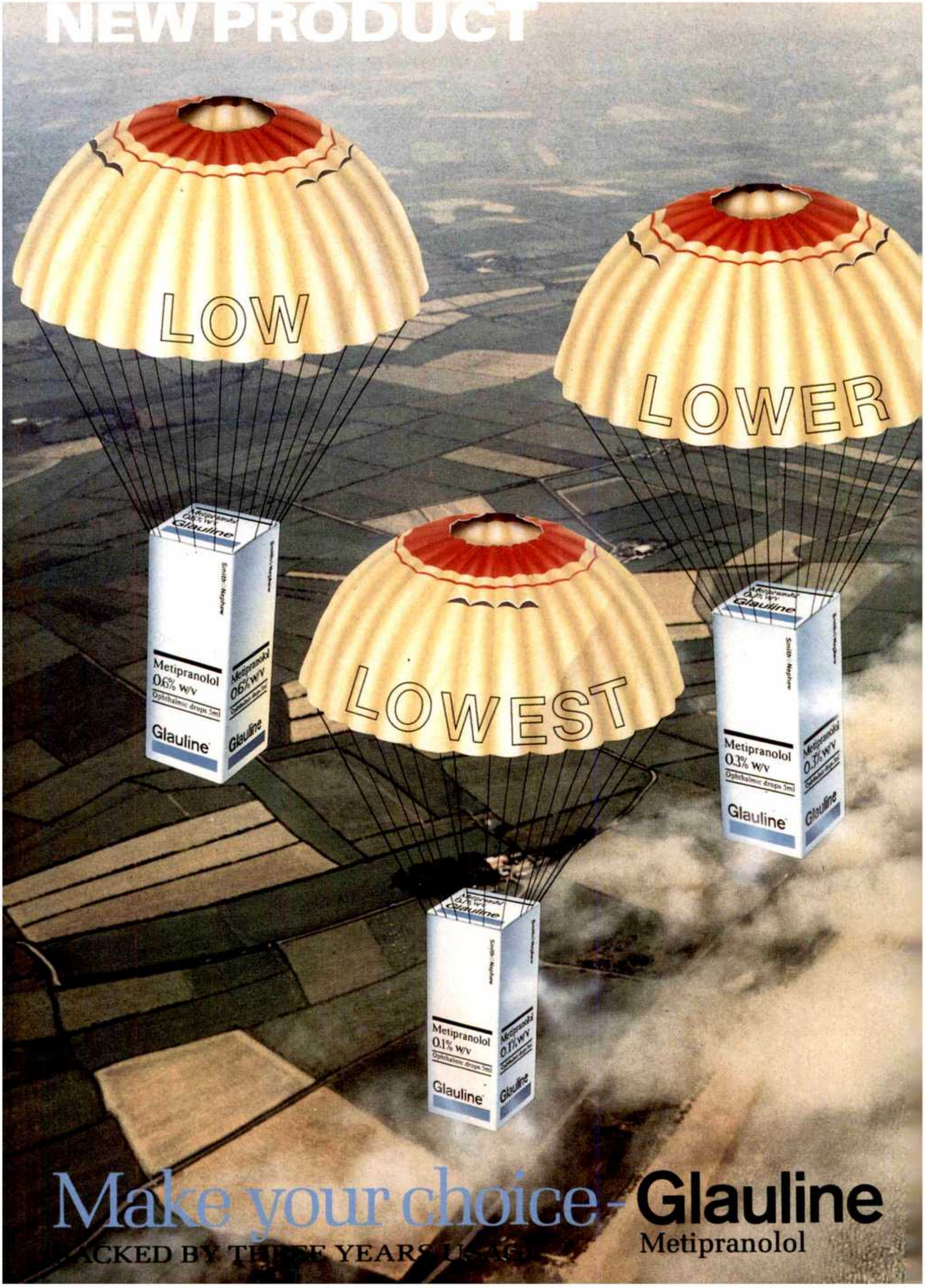
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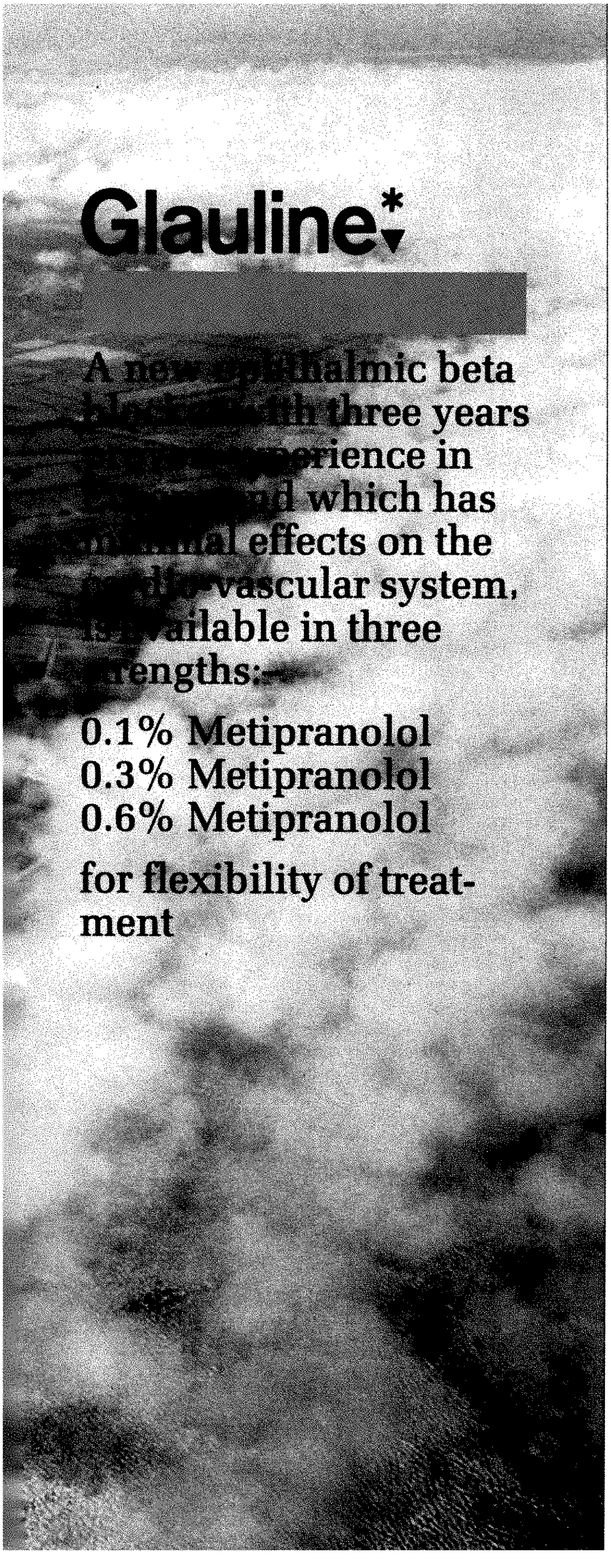

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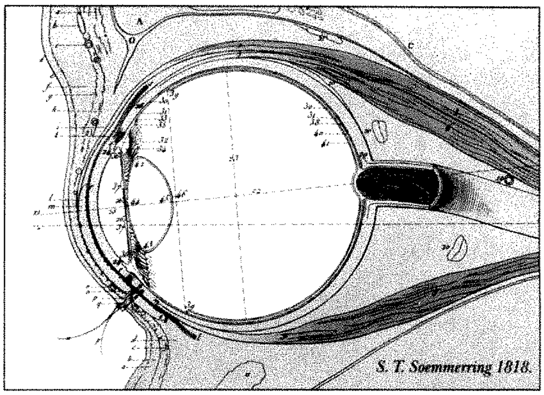

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British Journal of Ophthalmology, 1987, **71**, 215–219

Modern cataract surgery in a highly myopic population

K A GROSS AND J L PEARCE

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SUMMARY A retrospective series of 117 highly myopic eyes with extracapsular cataract extractions and posterior chamber lens implants is presented. The results are analysed with reference to the current understanding of the complications anticipated. Of particular note is the use of low-powered posteriorly vaulted posterior chamber implants, with and without primary posterior capsulotomy. The results show a low retinal detachment rate (one eye, mean follow-up 12 months); low induced astigmatism (average 0·86 D); low myopic postoperative refraction (median −1·0 D); and high patient satisfaction.

Irvine,[1] in his article on the pathogenesis of aphakic retinal detachments, reminds us of A C Hilding's work of 1954 on the inertial vitreous traction inherent in posterior vitreous detachment and high velocity ocular saccades. His article argues the importance of the posterior convexity of the lens in stabilising the vitreous. However, in his assessment of modern cataract surgery he does not discuss the results of posteriorly vaulted posterior chamber lenses following extracapsular cataract extraction.

To explore the possible advantages of these lens implants a retrospective review was made of all cataract surgery performed in the Mid Worcester District Health Authority over the years 1982–4 inclusive.

Materials and methods

POPULATION

During this three-year period 1235 cataract extractions were performed in the district. In 117 of these a calculated intraocular lens implant (IOL) of ≤16·0 dioptres (D) was fitted. In a further 89 cases lenses with powers of 16–18·0 D were used. It should be noted that the posterior vaulting and biconvex form of the optic mean that the lens's nodal point is placed 5·0–5·1 mm from the corneal surface. A comparable 'iris plane' lens would have a 3·5–4·0 D lower power. We are thus discussing a sample of highly myopic eyes.

SAMPLE

The notes of all 117 patients were reviewed at a maximum of 44 months and a minimum of 9 months after operation. Their average age was 69·2 years, with a maximum of 90 and a median of 71 years. There were two notably younger patients (17 and 23 years), one having Down's syndrome, the other having congenital cataract with nystagmus.

The preoperative corrected visual acuity with high myopic refraction was 6/36 or less in 48% of patients. A subgroup of 16 patients had vision of 6/12 or better. All had rapidly advancing myopic nuclear sclerosis, focal posterior cataracts, or contralateral pseudophakos. The mean spherical equivalent correction averaged −10·0 D, with a standard deviation of 1·08 D (Fig. 1).

The average axial length in this group of patients was 27·34 mm, SD 0·15 mm. The maximum measurement was 32·3 mm. In one patient the axial length was 23·6 mm, and the eye was implanted with a 16·0 D lens owing to an abnormally high corneal refractive power. This patient was eliminated from the follow-up as he would not carry the same high risk factors associated with axial myopic cataract extraction. The minimum axial length was thus 24·9 mm (Fig. 2).

SURGERY

All patients underwent non-automated extracapsular cataract extraction with no peripheral iridectomies. Sodium hyaluronate 1% (Healonid) was used in all operations. 1 ml of 0·75% bupivacaine retrobulbar injection (in addition to general anaesthesia) was given routinely, though six patients were limited to a local anaesthetic alone in view of their poor general health. 73% received primary posterior capsulotomies prior to the insertion of the posteriorly vaulted,

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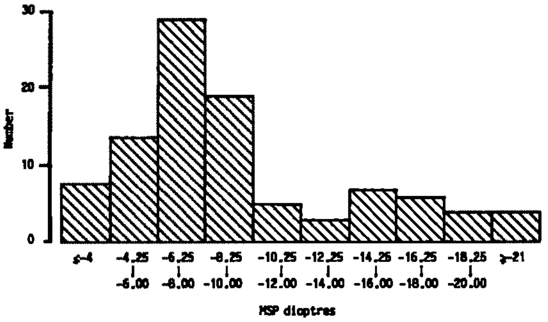

Fig. 1 *Distribution of the mean spherical equivalents of the preoperative refraction.*

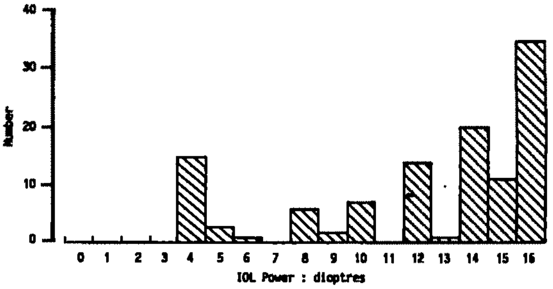

Fig. 3 *Distribution of intraocular lens's powers used in these patients. Note peak at 4·0 D due to the lack of available low power lenses at that time.*

posterior chamber lenses, which included 63 J Pearce tripods, 43 J Pearce Y loops, and nine other miscellaneous posterior vaulted IOL. Twenty-eight patients underwent bilateral cataract surgery, and five patients underwent a combined cataract/trabeculectomy procedure.

The powers of the lenses used are shown in Fig. 3. These were influenced by availability, particularly the absence of lenses of less than 4 dioptres at that time.

Patients were routinely discharged the following day on guttae dexamethasone 2-hourly, with miotics if necessary. It should be noted that no eye received prophylactic retinal treatment (cryotherapy etc.) prior to surgery.

Results

A minimum period of three months documented follow-up was specified. This eliminated seven patients owing to: death (1), return abroad (2 patients with favourable reports by letter subsequently), failure to attend (2), and return to distant UK homes (2). Two further patients were eliminated owing to abandoned implantation peroperatively. One patient suffered a posterior dislocation of the implant into the vitreous at four days (vision 6/6 after 12 months with no additional complications). With the patient eliminated previously (axial length of 23·6 mm), this left 106 patients for analysis.

The average period of follow-up for which full notes were available was 12·3 months, with a maximum of 36, a minimum of 3, a median of 12, and a standard deviation of 1·14. Thus there were 54 patients with a greater than 12-month follow-up (average 19·5 months).

The visual acuity of these patients, who were lifelong myopes, improved to ≥6/12 without glasses in 40·5% of cases; 83·6% achieved a vision in excess of 6/12 with glasses (Figs. 4, 5). Direct comparison with the levels of vision achieved in uncomplicated cataract surgery (93+% ≥6/12[2,3]) is not possible in view of the degenerate retinal function in high myopia.

Eleven patients achieved ≤6/36 (8·6%), and it is conspicuous that nine of this group (81·8%) had an axial length >28 mm (in the whole sample only 28% had an axial length >28 mm). This was a significant finding (Student's t test, $p \leq 0 \cdot 01$). Nine of these patients had gross preoperative myopic macular degeneration (or senile macular degeneration), two with coexistent chronic simple glaucoma (CSG), and

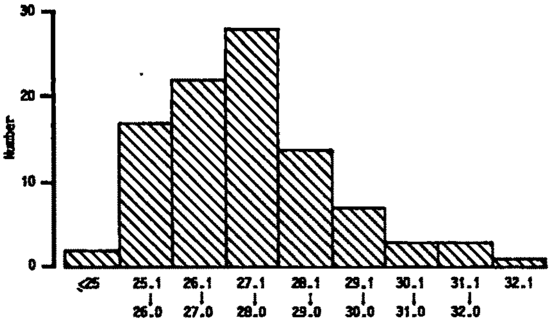

Fig. 2 *Axial lengths as recorded with various A scan ultrasounds.*

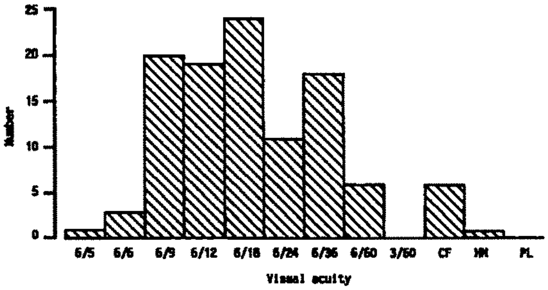

Fig. 4 *Visual acuity recorded without glasses at one month after operation.*

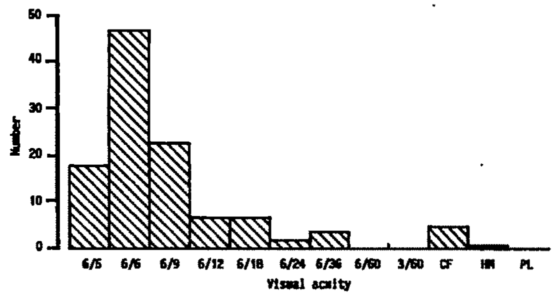

Fig. 5 *Visual acuity recorded with glasses at more than three months after surgery.*

one had CSG alone. One patient had proliferative diabetic retinopathy despite the relative protection that myopia is believed to afford to diabetic fundi.[4 5]

The mean spherical equivalent of the postoperative correction at more than three months, averaged −0·76 D with a median of −1·0 D. 69·5% had ≤2·0 D spread around the desired postoperative refraction of −1·0 D (Fig. 6). 10·5% had a >3·0 D error range. It is perhaps noteworthy that not all patients could be calculated for the optimum optical result[6] owing to the existing refraction of the other eye and/or the availability of specific lens powers. A minor trend of increasing myopia during the first month after operation was found to be statistically not significant.

Surgical astigmatism averaged 0·86 D at three months plus, after operation. 72·5% had a cylinder of <1·0 D, and 6% had >2·0 D. A significant ($p < 0{\cdot}05$) decrease in astigmatism over the first three months was noted. 91% of eyes were noted to have the posterior capsule sealed against the posteriorly convex implant surface, with or without a primary capsulotomy.

COMPLICATIONS

The peroperative problems were restricted to the two cases mentioned in which implantation was abandoned because of posterior capsular tears and vitreous loss. Of these one has <6/60 due to myopic degeneration, but has been followed up for 18 months without further complications. The other has had a two-year follow-up with 6/9 corrected vision. In the immediate postoperative period there were minor complications of residual soft lens matter (6), small hyphaemata (2), and small anterior chamber vitreous prolapses (4). These complications showed a decreasing incidence with greater surgical experience, and 10 out of the 12 achieved >6/12 vision.

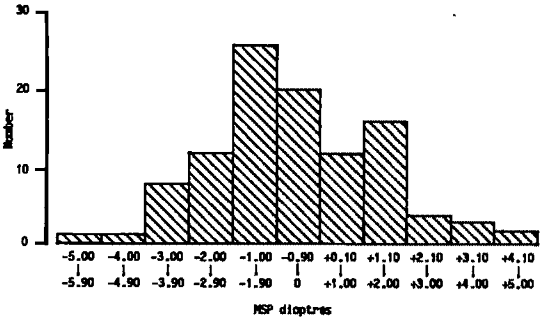

Fig. 6 *Distribution of mean spherical equivalents of the postoperative refraction.*

One patient suffered a posterior dislocation of the implant into the inferior vitreous within four days of surgery. There have been no additional complications in this patient, who retained 6/6 vision at 12 months follow-up, using a contact lens.

Long-term complications included opacification of the posterior capsule in 11 patients, sufficient to require a secondary capsulotomy. Six of these had had what was presumably a non-axial, primary capsulotomy. There were no cases of pupil trap, presumably owing to the posterior vaulting of the IOL giving a good clearance from the miosed pupil. Some distortion of the pupil was noted in three cases from anterior capsule tags or vitreous. One patient developed decentration of the posterior chamber lens, secondary to capsular fibrosis, although the optic remained in the visual axis, permitting near normal function.

There have been no cases of 'clinical cystoid macular oedema' (CMO), infection, severe inflammation, or corneal decompensation.

There has been one case of postoperative retinal detachment. This occurred in a patient who had had no obvious surgical problems. He presented with a posterior, large U-shaped retinal tear in lattice degeneration following a posterior vitreous detachment occurring 18 months postoperatively. Simple radial plombage has reattached the retina with retained vision of 6/12. This is the pattern of a phakic as opposed to an aphakic retinal detachment (both in appearance and in response to treatment). The good surgical prognosis of retinal detachment surgery following extracapsular cataract extraction with posterior chamber lenses has been previously noted.[7 8]

Discussion

This sample, extracted from the cataract surgery performed over a three-year period, was designed to be among the highest-risk surgical population. A multitude of surgical series demonstrate the greatly increased risk of aphakic retinal detachment in axial myopia.[9–12]

The poor Snellen visual acuities achieved in nine of 13 patients with preoperatively identified 'myopic/senile' degeneration should not obscure the very real improvement in these patients' undistorted peripheral vision. In addition four of the 13, who might have been denied surgery because of their known macular degeneration, achieved better than 6/18.

Irvine[1] has eloquently discussed the various known mechanisms of aphakic retinal detachment, notably the inertial vitreous traction present with horizontal ocular saccades. He summarises the results of different surgical techniques, but stops short of discussing posterior vaulted, posterior chamber implants. This is the very modification most likely to reproduce the vitreous support of the posterior convexity of the crystalline lens.

His article also comments on the increased risk of retinal detachment with primary posterior capsulotomy, possibly due to loss of hyaluronic acid from the vitreous[13] and unplugging of small retinal holes. The intraocular lenses used in this series of patients, being posteriorly vaulted and having a posteriorly convex optic, achieved a 'seal' against the posterior capsule (and capsulotomy) in 91% of cases. These lenses have now been in use for more than five years, and our experience of them warrants wider discussion.

The low incidence of aphakic retinal detachment (ARD) in this group of patients so far is very reassuring, as 67·7% of such detachments occur in the first year after operation (cumulative figure: 44 of 65 ARD[9 10 12 14]). The incidence of retinal detachment in myopic cataract extractions varies from 7% to 40%.[9 10 12] This latter figure comes from a myopic population with a spectacle correction of greater than −10 D (42% of our sample).

The retinal detachment incidence following all extracapsular cataract extractions and posterior vaulted, posterior chamber lenses at the Bromsgrove General Hospital is currently 0·167% (Pearce JL, unpublished data). This is entirely compatible with other large series previously reported (0–2·2%[12 14]) though the very low incidence of this complication in the normal postcataract population makes comparison between published series difficult.

'Clinical' CMO is suspected when an eye, after cataract extraction, suffers a fall in visual acuity one month or more after operation. Such a patient would then undergo fluorescein angiography to confirm the diagnosis. The high incidence of subclinical, thus irrelevant, CMO is not disputed.[15-18] The 'sealed' primary capsulotomy reduces our 'clinical' CMO incidence to that of intact posterior capsule surgery. With the increasing availability of YAG lasers during 1985 the slightly higher surgical risks of primary capsulotomy have led to a decrease in the indications for its use.

A 2–3 mm stepped scleral lamellar flap with a 10 mm chord length is used in all extracapsular surgery at this unit (Fig. 7). Extremely short radius, deep 10/0 nylon sutures are employed to achieve a consistently low cylinder while providing a secure wound. The surgical astigmatism achieved with this section compares well even with series designed to show the advantages of using operating keratometers.[19]

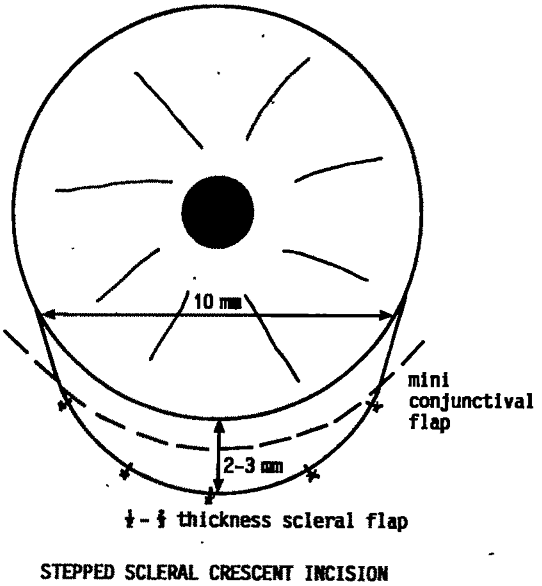
10 mm
mini conjunctival flap
2–3 mm
½ - ⅔ thickness scleral flap
STEPPED SCLERAL CRESCENT INCISION

Fig. 7 *Surgical incision and closure used routinely in this population. Notable features are the increased distance from the cornea, very short bite sutures, and obvious potential for combined cataract/drainage surgery.*

CONCLUSION

The use even of low power, capsule-fixated intraocular lenses may be considered for all myopic cataract extractions. They have few additional complications associated with their use over those of cataract surgery alone.[20] Their possible advantages include: the pronounced preference of patients for mild myopic refraction over even low grade aphakic hypermetropia[21]; the avoidance of aphakic visual field distortion in patients whose macular function is already compromised; and finally the theoretical protection against aphakic retinal detachment afforded by a near physiological posterior capsule convexity. This latter contention is supported by our series and others.[3 21]

We acknowledge with thanks the expert advice of Mr M J Roper-Hall and Mr R Brown, and thank Mrs D Thomas for the preparation of the illustrations.

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Bietti's tapetoretinal degeneration with marginal corneal dystrophy (crystalline retinopathy): case report

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SUMMARY A patient with Bietti's tapetoretinal degeneration and marginal corneal dystrophy is reported on. Refractile deposits found in both the retina and cornea are the most striking feature of this condition. Apart from a slight reduction in left visual acuity there were no visual symptoms. The dark adapted electroretinogram was abnormal. No metabolic disturbance was detected.

A tapetoretinal degeneration combined with a marginal corneal dystrophy was described by Bietti in three patients (two of whom were brothers) in 1937.[1] The fundus picture was reported to be similar to that of retinitis punctata albescens, but the spots, located mainly at the posterior pole, were refractile, polygonal, and could be seen at all levels of the neuroretina. Pigment changes were seen at the fovea and the retinal periphery. The corneal deposits were numerous, very small, yellowish white, and concentrated in the superficial layers of the cornea near the limbus. Eight similar cases have since been reported,[2,3] and the term crystalline retinopathy has been applied to the fundus appearance.[3] Our case is the first to be reported in Britain.

Case history

A 23-year-old Caucasian woman attended her optician for a routine refraction. She had no visual symptoms and the visual acuity was recorded as 6/5 in each eye. Some pigmentary changes were noted at both maculae, and on referral to an ophthalmologist the retinal findings were confirmed, though no further action was taken. Six years later she became aware of slight reduction in her left visual acuity and was reassessed.

Her history was unremarkable. She was the only child of unrelated parents and there was no family history of any ocular disorder. Apart from allergic rhinitis her health was excellent. Dietary habits were normal and she was not taking any regular medication. There was no history of night blindness.

On examination her visual acuities were 6/5 right and 6/6 left unaided. Fine dot-like opacities were present in the superficial layers of the corneal stroma at 360° of the limbus in both eyes. These opacities had the appearance of tiny crystals (Fig. 1). The anterior segments were otherwise normal. Examination of the fundi showed pigment clumping at both maculae, more marked on the right than on the left. Yellowish white crystalline deposits were scattered over the posterior poles of both eyes. They were detected in all layers of the neuroretina and some lay in front of blood vessels (Fig. 2, 3). Small clumps of retinal pigment extended to the equator, but the retina beyond the equator appeared normal (Fig. 4). Visual fields were full (Friedman field analyser and Goldmann perimeter), and colour vision was normal (100 hue test).

Fluorescein angiography showed atrophy of the retinal pigment epithelium at both posterior poles, with an intact choriocapillaris and normal retinal vasculature. The crystalline deposits did not fluoresce (Fig. 5).

Electrodiagnostic tests revealed normal 'a' and 'b' waves of the electroretinogram (ERG) of both eyes during light adaptation in terms of both latency and amplitude. The electro-oculograms (EOGs) were also normal in both eyes. The ERG of both eyes and the electroencephalogram (EEG) followed flickering light up to 64 Hz. The 'b' scotopic wave of the ERG of

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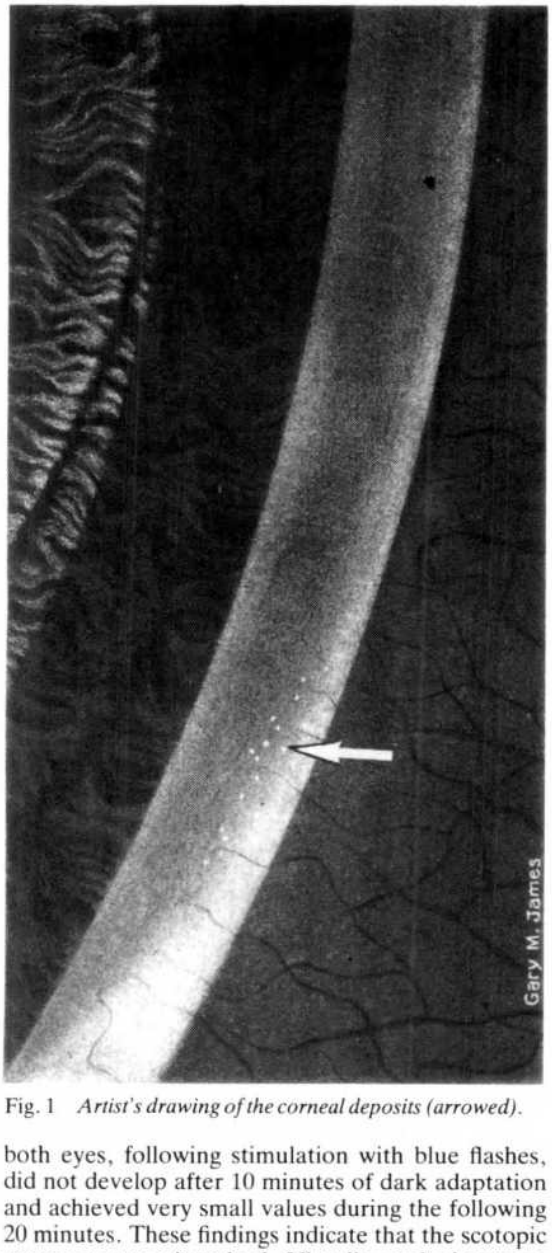

Fig. 1 *Artist's drawing of the corneal deposits (arrowed).*

both eyes, following stimulation with blue flashes, did not develop after 10 minutes of dark adaptation and achieved very small values during the following 20 minutes. These findings indicate that the scotopic responses were impaired. Visually evoked pattern reversal responses were normal.

A search of an underlying metabolic disorder was unrewarding, as the results of all the following investigations were normal: plasma urea, electrolytes, and creatinine; plasma and urine amino acid screens; fasting plasma triglyceride and cholesterol; quantitative lipoprotein assays. The 24-hour urine oxalate excretion was 0·12 mmol, which is low.

A number of lysosomal enzymes involved in glycolipid and oligosaccharide metabolism were assayed in leucocytes and in cultured skin fibroblasts. These were β-galactosidase, hexosaminidase A and B, β-glucuronidase, α-fucosidase, α-mannosidase, and aryl sulphatase. No abnormality was found, indicating that Bietti's disease is probably not a previously unrecognised lysosomal storage disorder.

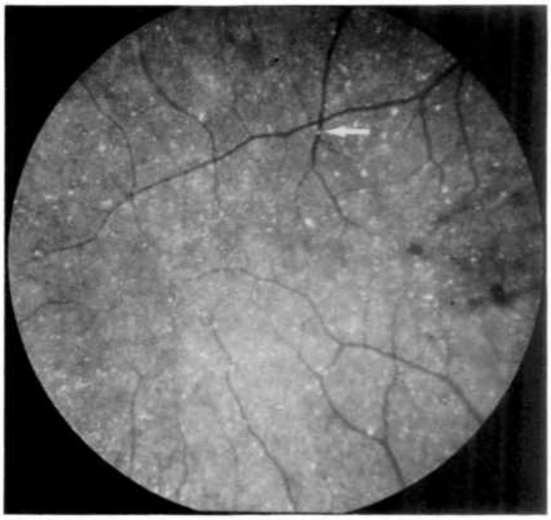

Fig. 2 *Fundus photograph of the right eye, showing macular pigmentary changes and numerous crystalline deposits, some lying in front of blood vessels (arrowed).*

Discussion

The clinical picture of a marginal corneal dystrophy and crystalline retinopathy provides little latitude with regard to the differential diagnosis, as few conditions show refractile bodies in both cornea and retina. The crystals of cystinosis are found throughout the entire cornea, not solely at the limbus, and appear in the choroid and retinal pigment epithelium but not the neuroretina.[4] Corneal abnormalities have not been noted in cases of crystalline retinopathy of known cause, but they may have been overlooked. White retinal flecks, confirmed as oxalate crystals at necropsy, have been seen in a few patients with primary oxalosis[5] and in a patient with oxalosis secondary to prolonged methoxyfluorane anaesthesia.[6] There was no evidence of primary or secondary oxalosis in our patient. Refractile bodies may be found in the retina in cases of gyrate atrophy,[7] the Sjögren-Larsson syndrome,[8] and in patients treated with tamoxifen,[9] but the underlying condition is evident from the clinical history and examination.

The nature of the refractile deposits and any underlying metabolic abnormality in Bietti's disease remains unknown. A patient with hypobetalipopro-

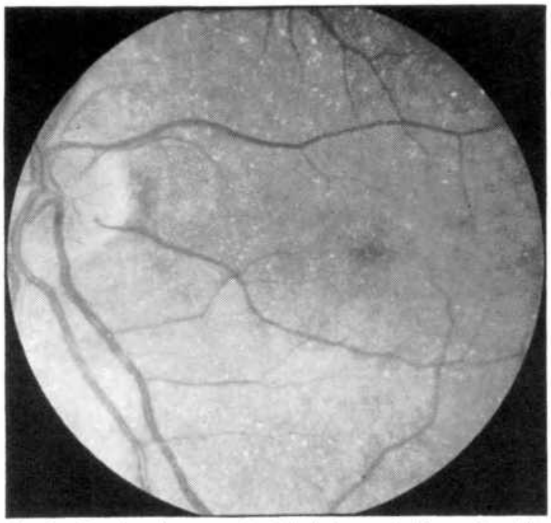

Fig. 3 *Fundus photograph of the left eye, similar to the right but with less obvious macular pigmentary changes.*

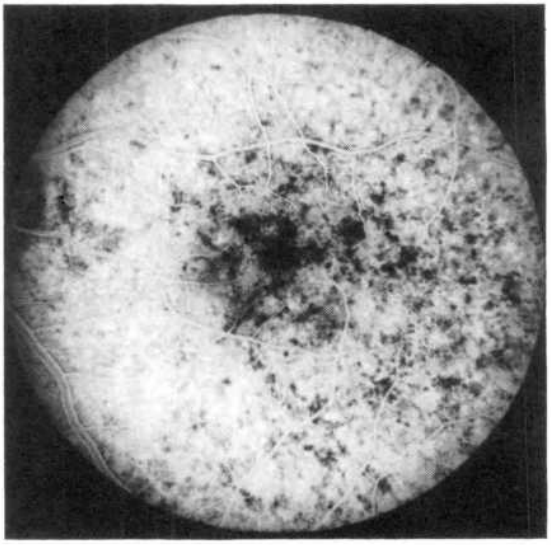

Fig. 5 *Fluorescein angiography of the left eye, showing retinal pigment epithelial changes only.*

teinaemia had a fundus picture said to resemble a crystalline retinopathy,[10] but three patients with Bietti's disease had raised serum cholesterol[1 2] (it is low in hypobetalipoproteinaemia) and the remainder had normal serum lipids and lipoproteins.[2 3] Two patients underwent corneal and conjunctival biopsy. Lipid inclusion bodies were found in the corneal and conjunctival fibroblasts and in a few corneal epithelial cells in one case, but no refractile deposits were seen.[3] The other biopsy was reported as normal.[2]

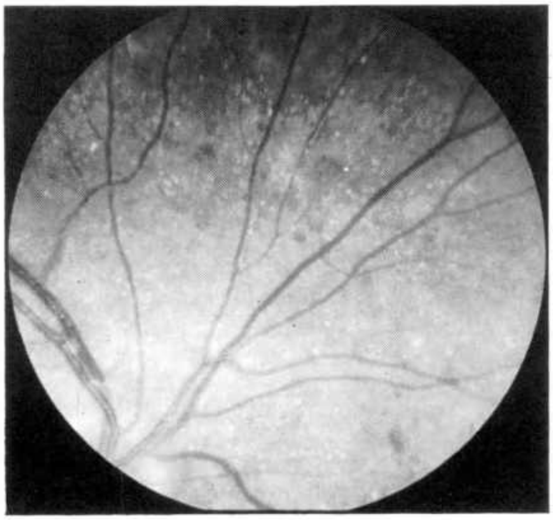

Fig. 4 *Fundus photograph of the right eye, showing crystalline deposits and peripheral pigmentary changes.*

There are considerable differences in the degree of retinal dysfunction in the reported cases of Bietti's disease, partly due no doubt to the progressive nature of the disorder, but as more cases are reported the parameters of clinical severity may become more evident. Long term follow-up of only two cases has been reported.[2] The two brothers originally seen by Bietti were re-examined by Bagolini and Ioli-Spada 30 years later. Both had suffered a marked decline in central vision and a contraction of visual field. The corneal dystrophy was unchanged, but the chorioretinal degeneration had advanced, though the number of crystalline deposits had decreased. The discs were slightly pale, and the retinal vessels were narrowed.

There are insufficient cases of Bietti's disease to establish a pattern of inheritance, if any, but the presence of two sibships and the child of a consanguineous marriage among the 10 reported cases[1 2] suggests an autosomal recessive disorder. Five cases of crystalline retinopathy similar to Bietti's but without the corneal dystrophy have been reported.[11-13] The presence of sibships and consanguinity within this group also suggests an autosomal recessive disease, but at present we do not know whether these cases share a common aetiology with Bietti's disease or merely show a clinical similarity.

We thank Angela Hobley and Dr Charles Pennock for their assistance, Jill Bennerson for the photographs, and Gary James for the drawing (Fig. 1).

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Lipofuscin and melanin content of the retinal pigment epithelium in a case of Sjögren-Larsson syndrome

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SUMMARY Necropsy material from the eye of a 23-year-old male known to have suffered from the Sjögren-Larsson syndrome, characterised by mental retardation, spastic diplegia or tetraplegia, congenital ichthyosis, and so-called glistening dots in the foveal and parafoveal areas of the fundus of the eye, was investigated ultrastructurally. The retinal pigment epithelium in the macular area showed a significant increase in lipofuscin granules, most likely because of a reduced capacity for digestion of phagocytosed material, and a significant decrease in melanin and melanolipofuscin granules in comparison with a normal control material. The ophthalmoscopically visible glistening dots and the pigment epithelial 'windows' seen on fluorescein angiography may possibly be explained by a further progression of these changes. No retinal changes were found in the macular area, the midperiphery, or the periphery that could be attributed with certainty to any other origin than post-mortem autolysis. More material would be needed, however, to elucidate further the fundal changes in the Sjögren-Larsson syndrome.

The Sjögren-Larsson syndrome, which is inherited in an autosomal recessive mode, is characterised by mental retardation, spastic diplegia or tetraplegia, and congenital ichthyosis.[1] In addition specific ocular fundal changes are found,[1] later described as 'glistening dots,' located in the foveal and parafoveal areas surrounding the foveola.[2-4] Jagell *et al.*[4] found such slightly elevated glistening dots in all 30 patients who were subjected to fundal examination.

In fluorescein angiograms of their case Gilbert *et al.*[2] observed increased transmission of the choroidal vascular pattern in scattered flecks within the macula, possibly indicating pigment epithelial 'windows.' In the same case the electroretinogram a and b waves were normal.[2] The electro-oculogram (EOG) was normal in two patients subjected to this investigation.[4] Conjunctival and corneal changes are considered to be part of the ectodermal disease. It has been suspected that the Sjögren-Larsson syndrome is associated with faulty metabolism of essential fatty acids.[5]

The present paper reports on ultrastructural findings in the retina and pigment epithelium of an eye obtained as necropsy material from a subject with the Sjögren-Larsson syndrome.

Material and methods

The eye was enucleated at necropsy of a 23-year-old male known to have suffered from the Sjögren-Larsson syndrome. After removal of the cornea the eye was immersed in 2·5% buffered glutaraldehyde solution about 10–11 hours post mortem. After one week's fixation, the eye was cut into smaller pieces and postfixed in 1% osmium tetroxide in Veronal acetate buffer. Pieces of retina from the posterior pole, the midperiphery, and the periphery were dehydrated and embedded in Vestopal W. Thin sections were stained with uranyl acetate and lead citrate and examined in a Philips EM 300 electron microscope. Because of pronounced retinal detachment in the midperiphery and periphery, the pigment epithelium was studied only in the posterior pole.

For analysis of the content of lipofuscin, melanin, and melanolipofuscin granules, sections of pigment

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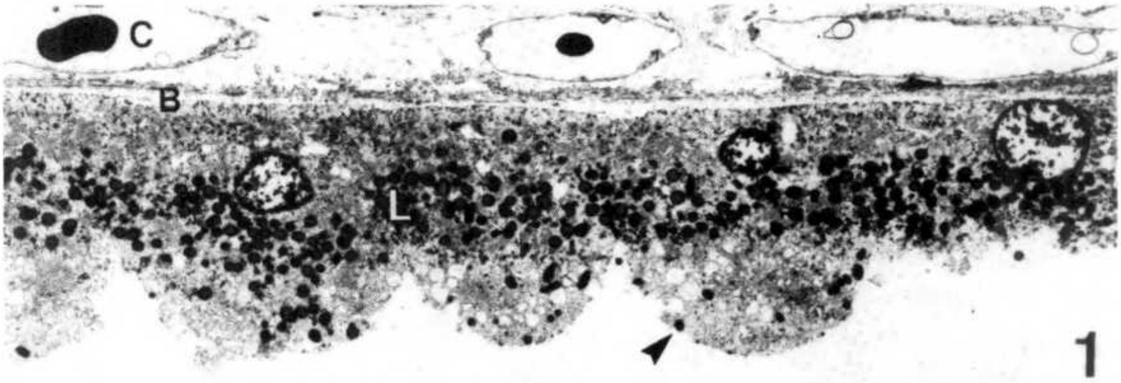

Fig. 1 *Retinal pigment epithelium from a 23-year-old male with Sjögren-Larsson syndrome. Post-mortem material. A large number of lipofuscin granules* (L) *and fairly few melanin granules (arrowhead) are seen.* B: *Bruch's membrane.* C: *choroidal capillary.*

epithelial cells were photographed at 3000 times magnification. The micrographs were printed at ×2·5. Montages of 15 contiguous pigment epithelial cell profiles were made from five different locations within the macular area.

Results

In spite of fairly extensive sectioning within the posterior pole, the midperiphery, and the periphery we did not find any retinal changes that could be

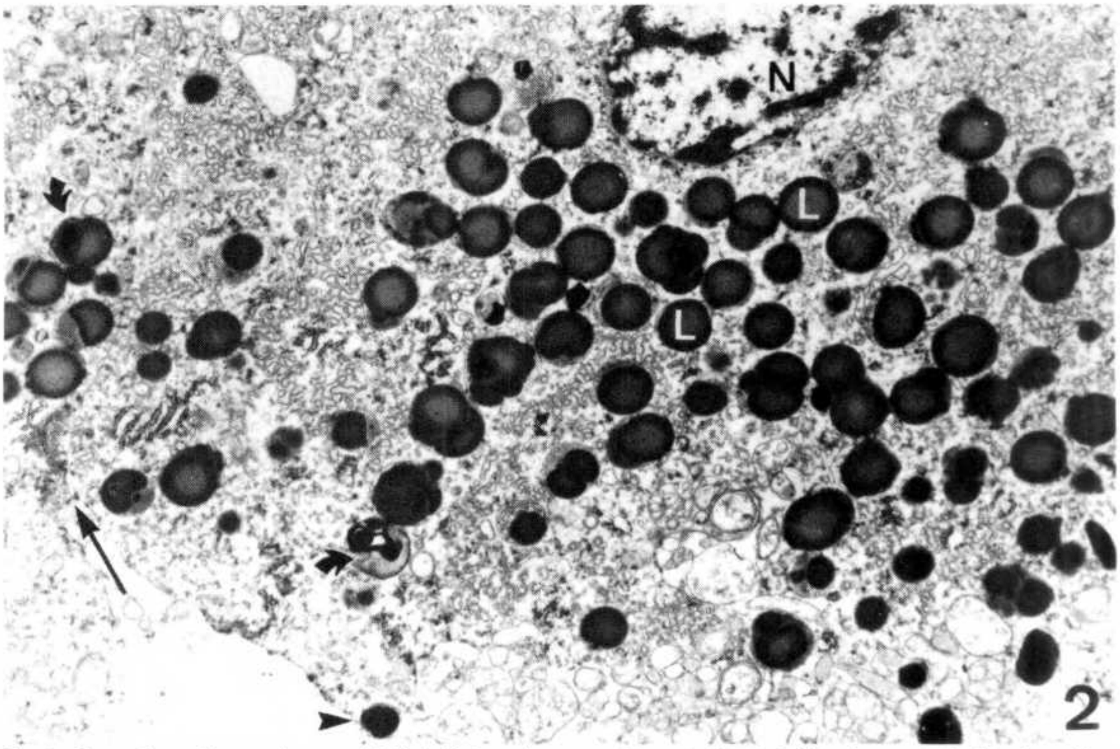

Fig. 2 *Parts of two adjacent pigment epithelial cells from the same subject as in Fig. 1. Cell border at apical side indicated by long arrow. Abundant lipofuscin (moderately stained) granules* (L), *but much fewer melanin (totally black) granules (arrowhead) and melanolipofuscin (combinations of the two other types) granules (short arrow).* N: *nucleus.*

attributed with certainty to anything but post-mortem autolysis.

The pigment epithelium of the posterior pole showed, in addition to post-mortem changes, a very high content of lipofuscin but a fairly low content of melanin (Figs. 1 and 2). The number of lipofuscin granules per cell profile was 55·6±2·4 (SEM), the number of melanolipofuscin granules 8·5±0·5, and the number of melanin granules 6·8±0·4. Many pigment epithelial cells were very voluminous, their apical part being rounded instead of more or less flat.

Discussion

Feeney-Burns *et al.*[6] performed careful morphometric analysis of the granular content of human pigment epithelial cells of eyes from each 10 decades of life. In the third decade, corresponding to the age of the present subject, the number per macular pigment epithelial cell profile of lipofuscin granules was about 15, the number of melanolipofuscin granules about 11, and the number of melanin granules 14·97±0·99 (SEM). The number of lipofuscin granules was significantly ($p<0·001$) higher (3–4 times), the number of melanolipofuscin granules significantly ($p<0·05$) lower, and the number of melanin granules significantly ($p<0·001$) lower in the subject with Sjögren-Larsson syndrome than in the control material provided by Feeney-Burns *et al.*[6]

The reason for the prominent increase in lipofuscin content may be a decrease in pigment epithelial capacity for digestion of lipofuscin (phagosomes), or an increase in phagocytosed material, or both. However, apart from post-mortem changes the photoreceptor outer segments did not seem to show any signs of degeneration, a fact that speaks against an increase in phagocytosis.

The histopathology of the glistening dots is unknown. The cause may be inclusions in the retina. No retinal inclusions have been found, but their presence cannot be excluded either. It is also possible, however, that a very heavy accumulation of lipofuscin may form the basis of these ophthalmoscopic changes. Although such heavy accumulations were not observed, they cannot be excluded.

An increased transmission of choroidal fluorescence was reported in a case of Sjögren-Larsson syndrome.[2] The low content of pigment epithelial melanin may contribute to such an effect, but a true 'window' would most likely require even fewer melanin and melanolipofuscin granules or a pronounced pigment epithelial atrophy. No such areas were found, but they cannot be excluded.

Thus the present paper demonstrates a significant increase in lipofuscin and a significant decrease in melanin and melanolipofuscin granules in the retinal pigment epithelium of a 23-year-old man with Sjögren-Larsson syndrome in comparison with normal conditions. The reason seems to be a reduced capacity for digestion of phagocytosed material. A further exaggeration of these changes may possibly explain the glistening dots seen on ophthalmoscopy. However, more tissue material would be needed to ascertain whether this is true, or if retinal changes are involved as well.

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Congenital iris cysts

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SUMMARY Unilateral, spontaneous, non-pigmented iris cysts appeared before the age of 2 years in four patients. Histopathological specimens obtained in three cases showed stratified to cuboidal, non-pigmented, epithelial lined cysts. Goblet cells were recognised in two of the three specimens. The clinical features and histopathological findings indicate that these cysts are derived from surface ectoderm and may be congenital.

Cysts of the iris have been divided into three groups: (1) acquired non-pigmented, (2) spontaneous non-pigmented, and (3) pigmented.[1] Acquired non-pigmented iris cysts arise from implanted surface epithelium months or years after penetrating ocular injuries or surgical procedures.[2] The time of onset of spontaneous or primary non-pigmented cysts is unclear, since often they are noted during general eye examinations. Spontaneous cysts are believed to be congenital, though they may not be detected until late in the first or second decade of life.[3,4] The clinical and histopathological appearances of spontaneous non-pigmented iris cysts is similar to that of acquired cysts. Pigmented cysts arise from the iris pigment epithelium, usually as a developmental anomaly. The clinical and histopathological appearance of pigmented iris cysts is quite distinct from that of non-pigmented cysts.[1]

The pathogenesis of spontaneous non-pigmented iris cysts is not clear. Proposed mechanisms include developmental entrapment of (1) surface ectoderm, or (2) neuroectoderm, or (3) surface ectodermal implantation secondary to occult trauma. Ectopic cystic lacrimal tissue also may occur within the iris stroma but is histologically distinct from non-pigmented iris cysts.[5,6]

Much of the confusion regarding the onset and aetiology of spontaneous non-pigmented iris cysts relates to their low incidence; hence the preponderance of single case reports.[1,3,4,7-12] Within the past 50 years published reports have rarely dealt with more than one case.[13] We report four cases of spontaneous, non-pigmented cysts of the iris.

Illustrative cases

CASE 1

A 4-year-old boy was seen at the University of Washington, Seattle, with a history of a non-traumatic iris cyst involving the inferonasal quadrant of the left eye. The child's mother had noticed a 'spot' on the left iris when he was 3 months old. At 4 months of age examination elsewhere established a diagnosis of iris cyst. Pregnancy and delivery were uncomplicated, and there was no history of amniocentesis or trauma. Progressive enlargement of the iris cyst had been noted since detection. During the previous 3–4 months the cyst had enlarged to involve the pupil, with resultant decrease in visual acuity from 20/30 to 20/60.

There was a 6 mm diameter transparent iris cyst filling the inferonasal quadrant of the anterior chamber (Fig. 1). The cyst wall showed overlying blood vessels that appeared to originate from the anterior chamber angle and adjacent iris. The fluid within the cyst was slightly turbid. The cyst touched the corneal endothelium, with mild stromal oedema over the area of contact. The underlying iris pigment epithelium appeared intact; however, the iris was adherent to the lens in the midperiphery. The remainder of the anterior chamber was deep and clear. The lens was clear. Applanation pressures were 12 mmHg in each eye. Ophthalmoscopic examination was normal.

Surgical excision was performed through a limbal incision. The iris cyst was densely adherent to the corneal endothelium in the inferonasal quadrant and extended into the peripheral angle. The iris pigment epithelium was adherent to the lens capsule in the inferonasal quadrant. The iris cyst was completely

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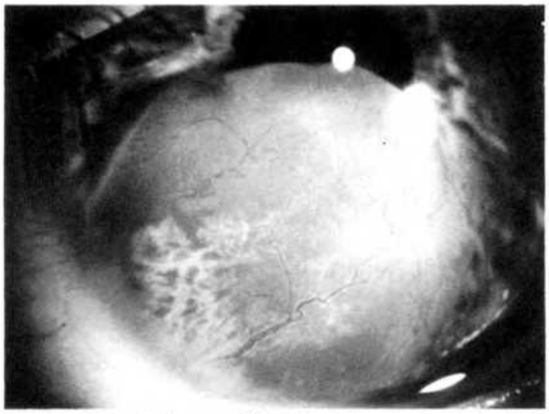

Fig. 1 *(Case 1). Iris cyst filling the inferonasal quadrant of the left anterior chamber. Prominent vessels arise from iris stroma and anterior chamber angle.*

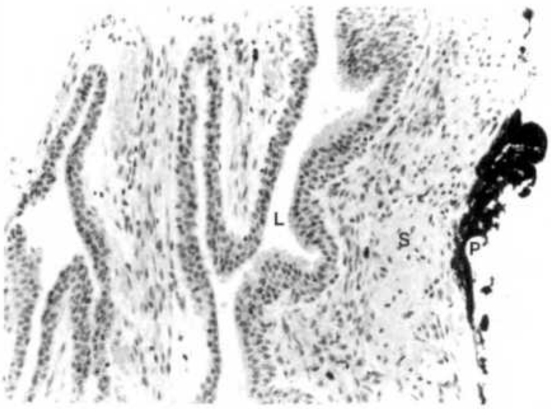

Fig. 3 *(Case 1). Collapsed wall of iris cyst, illustrating multilayered lining of epithelial cells.* L, *lumen of cyst;* S, *iris stroma;* P, *iris pigment epithelium. Haematoxylin and eosin.*

dissected from the cornea and the lens and excised. Cryotherapy by a double freeze-thaw technique was applied at the inferonasal limbus after filling the anterior chamber with air. Examination one year later showed no recurrence (Fig. 2). Visual acuity was 20/40.

Half of the specimen was fixed in Yanoff's solution, and processed in methacrylate for light microscopy and in Epon for electron microscopy. The other half was fixed in methyl Carnoy's fixative and processed in paraffin for immunocytochemistry. Light microscopy showed a two to three layered non-pigmented intrastromal epithelial iris cyst with numerous goblet cells (Figs. 3, 4). The stroma surrounding the cyst was fibrous, without inflammatory cells, but contained numerous congested vessels. Electron microscopy confirmed the presence of goblet cells (Fig. 5). Monoclonal antibodies to intermediate filaments gave strong reactivity to epithelial cytokeratin markers, but were negative for other antigens tested (muscle specific actin, smooth muscle actin, vimentin, human melanoma antigen, S-100 protein).

CASE 2

A 22-year-old woman was seen at Pacific Medical Center, Seattle, Washington, because of a recently irritated left eye. Examination at 2 years of age had revealed a small yellow-white spot of the left inferior iris. There was no antecedent history of birth or postnatal trauma. At age 21 an iris cyst was noted that did not contact the corneal endothelium.

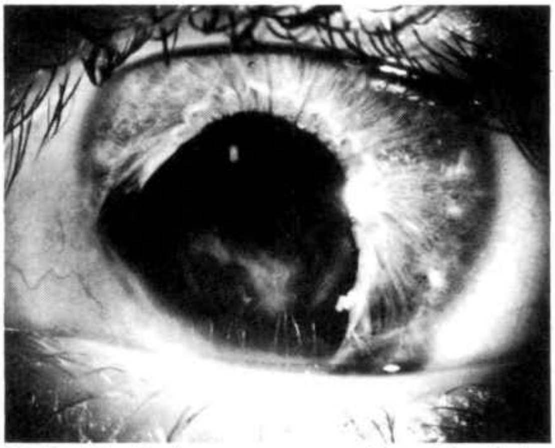

Fig. 2 *(Case 1). Appearance one year after excision of iris cyst. The visual axis is clear, but deep stromal corneal scarring is present.*

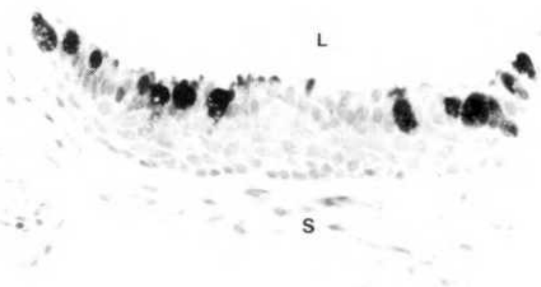

Fig. 4 *(Case 1). Densely stained goblet cells are evident in the epithelial wall of the cyst.* L, *lumen;* S, *stroma. Periodic acid-Schiff stain.*

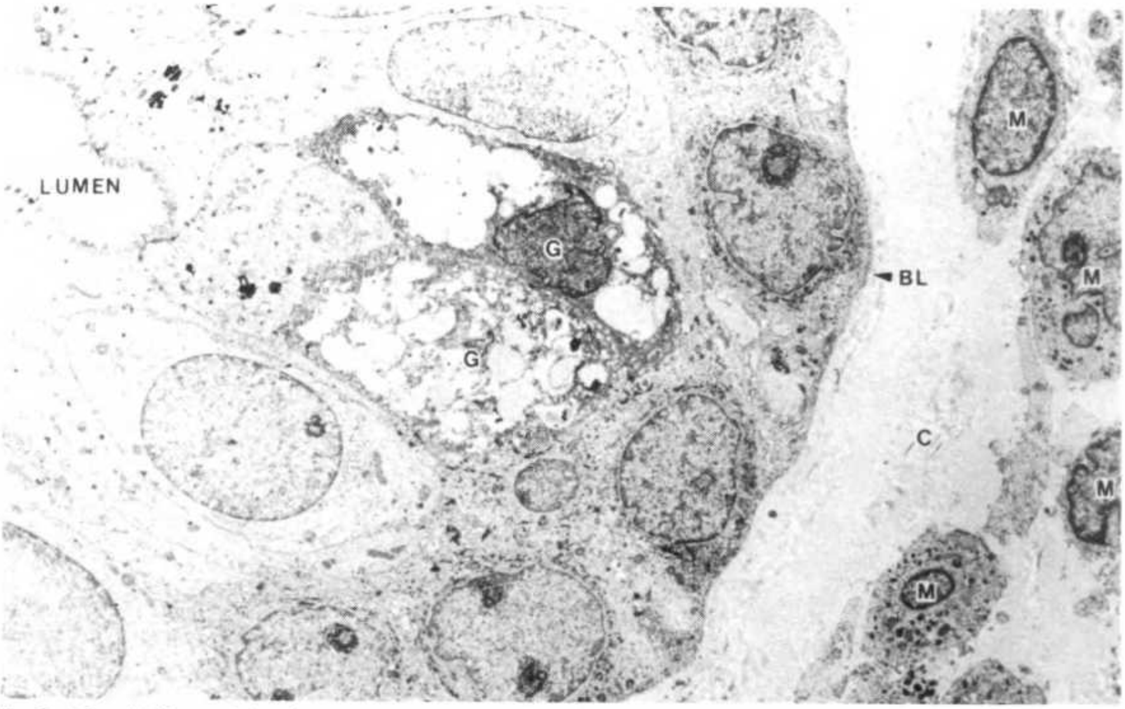

Fig. 5 *(Case 1). Transmission electron micrograph of wall of cyst, illustrating lumen, stratified epithelial cells resting on basal lamina* (BL), *and two goblet cells* (G). M, *stromal melanocytes;* C, *stromal collagen.*

Visual acuity was 20/20 OU. The right eye was normal. Left bulbar injection and photophobia were noted. The left cornea was clear; the anterior chamber was deep with 2+ cells and flare. A 4 mm iris cyst was present in the inferior anterior chamber (Fig. 6). The anterior surface of the cyst was translucent and contacted the corneal endothelium. The contents of the cyst were turbid, but there was no layered debris. The iris pigment epithelium appeared intact, and the lens was clear. Applanation pressures were 7 mmHg OD and 12 mmHg OS.

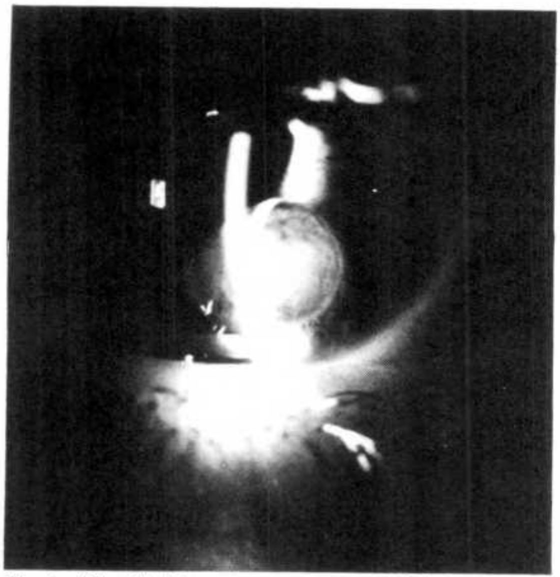

Fig. 6 *(Case 2). Iris cyst contacts cornea in left eye.*

The iris cyst was completely excised by surgical iridectomy via an inferior limbal approach. Corrected postoperative visual acuity was 20/20 and intraocular pressure remained at 12 mmHg OS. Follow-up at one year showed no recurrence.

The tissue was fixed in Yanoff's solution and processed in paraffin. Histopathological study showed a cyst wall of two-layered non-pigmented epithelium (Fig. 7) with occasional goblet cells apparent on PAS staining. Immunocytochemical studies with monoclonal antibodies to intermediate filaments yielded a positive reaction only to epithelial cytokeratin markers.

CASE 3

A 2-year-old boy was referred to the University of Washington for evaluation of recently recognised anisocoria. The pregnancy and delivery were uncomplicated, with no history of amniocentesis or birth trauma. There was no known history of ocular

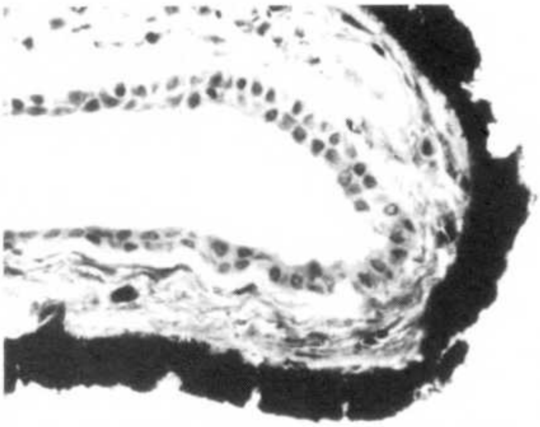

Fig. 7 *(Case 2). Two-layered non-pigmented epithelial-lined iris cyst. Haematoxylin and eosin.*

or head trauma. Initial examination showed central, steady, and maintained fixation bilaterally. The left pupil was 1 mm larger than the right and both reacted briskly to light. The left eye was normal. The right eye contained a transparent 2·5 mm cyst in the superonasal quadrant of the iris extending into the anterior chamber (Fig. 8). White debris was seen in the inferior part of the cyst. The anterior cyst wall was in contact with the cornea, causing mild stromal oedema. Careful review of family photographs showed the iris cyst to have been present by age 6 months.

Three months later the child developed photophobia and tearing, which responded to topical corticosteroids. The cyst appeared slightly larger at this time. Aspiration and injection of the cyst with trichloroacetic acid was performed at the University of Oregon. The cyst involuted initially but by age 4 years it was noted to have increased in size once again. Visual acuity was 20/25, and the child had intermittent, minor symptoms of photophobia and irritation.

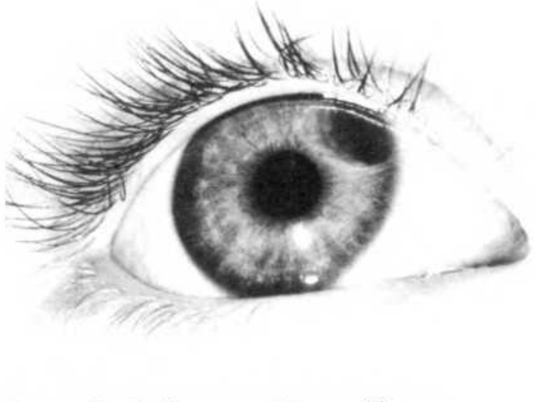

Fig. 8 *(Case 3). Transparent iris cyst, right eye.*

CASE 4

A 14-day-old boy was evaluated for a one-day history of an inflamed left eye. He was the product of a normal pregnancy and uncomplicated delivery, with no history of amniocentesis or trauma at birth. The right eye appeared normal. There was slight left eyelid erythema and oedema, with conjunctival injection. The left cornea was moderately oedematous and measured 10·0×10·5 mm (0·5 mm smaller than the right cornea). Tension by Schiøtz tonometry was normal in both eyes. A translucent cyst filled the inferior half of the anterior chamber, contacting the corneal endothelium and containing flocculent white material. Vessels extended from the iris over the anterior surface of the cyst. There was a faint transillumination defect of the underlying iris. Pigment could be seen on the anterior lens capsule; the lens itself appeared clear. No detailed view of the fundus was possible, but a red pupillary reflex was present, and ultrasonography of the posterior segment appeared normal.

The initial clinical impression was congenital iris cyst. Because of the significant ocular inflammation further investigations were thought to be indicated. Examination under anaesthesia and diagnostic paracentesis was performed at 18 days of age. Intraocular tensions by Perkins applanation was 11 mmHg OD and 13 mmHg OS. Aqueous fluid was withdrawn from the superior portion of the anterior chamber (away from the iris cysts) and submitted for cytological and microbiological examination. Cultures were negative and cytology revealed non-specific inflammatory response.

The inflammation and corneal oedema subsided with use of topical corticosteroids. Alternate day patching of the right eye was tolerated for six months. Recurrent episodes of inflammation occurred with cataract formation noted at 2½ years of age.

At 3 years of age a 2 cm mass was excised from the superonasal quadrant of the left orbit. Histopathological examination revealed a dermoid cyst consisting of stratified squamous epithelium with dermal appendages including pilosebaceous units.

At age 4 years marked photophobia and intermittent pain were present, with light perception vision OS. Clinical examination was remarkable for band keratopathy, cystic structure within the inferior two-thirds of anterior chamber, posterior synechiae, elevated intraocular pressure, and cataract. The left globe was enucleated and submitted to the Armed Forces Institute of Pathology in Washington, DC (AFIP Accession number 1927918).

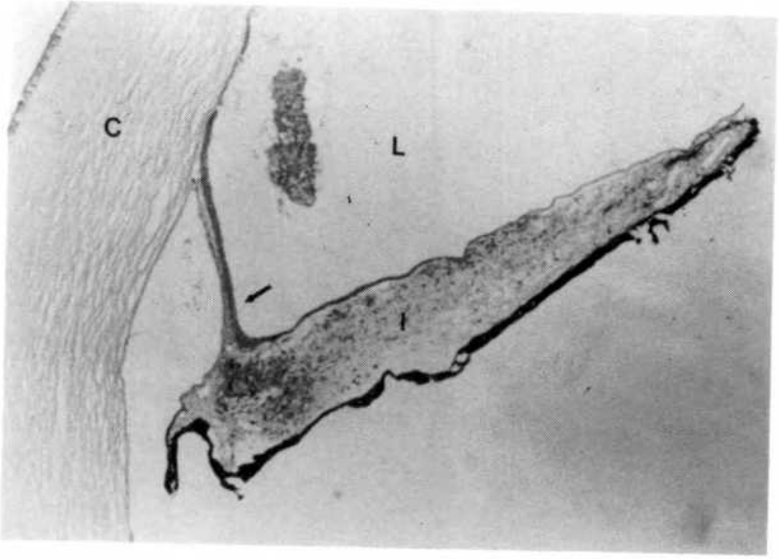

Fig. 9 *(Case 4). Portion of epithelial cyst (arrow) lining the inferior two-thirds of the left anterior chamber.* I, *iris;* C, *cornea;* L, *lumen. Haematoxylin and eosin.*

Light microscopy revealed a 1–3-cell layered non-pigmented epithelial cyst filling most of the anterior chamber (Figs. 9, 10). The cyst contacts both corneal endothelium and iris surface with areas of near-total iris stromal atrophy (Fig. 11). Goblet cells were not present. Cataractous lens remnants were present (Fig. 12). Mild optic atrophy was present.

Discussion

The aetiology of spontaneous or congenital non-pigmented iris cysts has been controversial. Early twentieth century reports suggest these cysts arise from displaced surface ectoderm during lens vesicle formation.[14–16] Some later authors have concurred,[7 10 12 17–19] while others have argued in favour of a neuroepithelial origin from the anterior portion of the optic vesicle.[3 9 20–25]

Histopathological specimens of spontaneous non-pigmented iris cysts typically consist of two to three layered squamous to cuboidal epithelium. Numerous reports demonstrate goblet cells,[7 8 10 12 13 17] while they are absent in a nearly equal number of reports.[3 4 9–11 13] The presence of goblet cells within some iris cysts clearly establishes surface epithelium as the cellular origin in those cases. The absence of goblet cells in

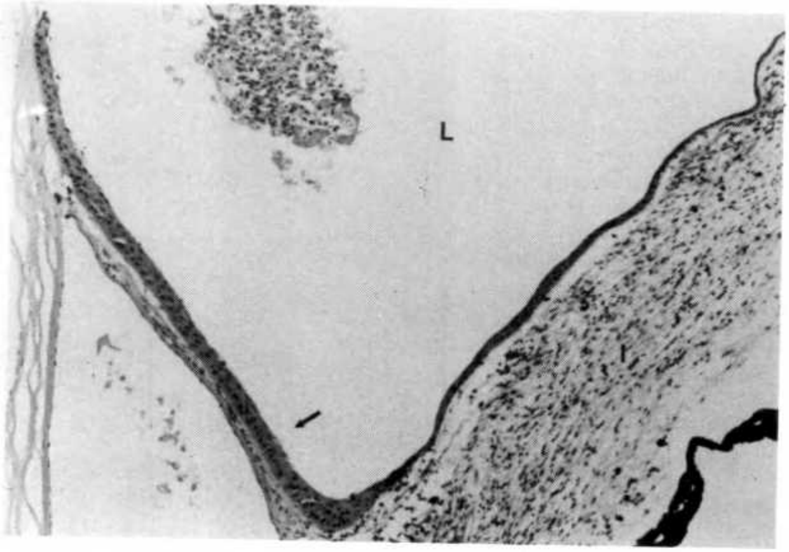

Fig. 10 *(Case 4). Squamous epithelial cyst (arrow) filling inferior anterior chamber of right eye.* I, *iris;* L, *lumen. Haematoxylin and eosin.*

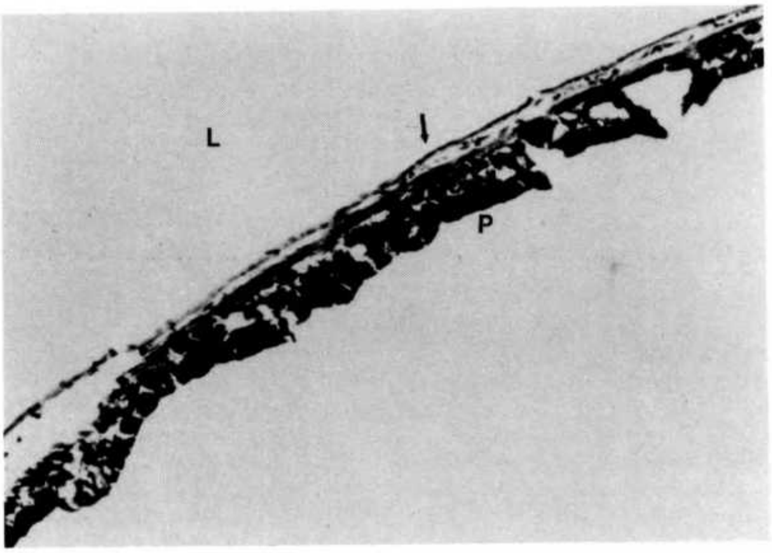

Fig. 11 *(Case 4). Part of cyst showing single epithelial layer (arrows) with nearly-total loss of iris stroma.* P, *iris pigment epithelium;* L, *lumen. Haematoxylin and eosin.*

spontaneous non-pigmented cysts raises the possibility of other cellular origins. It remains possible that more than one cellular origin and pathogenic mechanism exist.

Goblet cells were readily recognised in two of our three cases in which the histopathology was examined. Surface epithelium is undoubtedly the origin of these iris cysts; however, it does not establish the manner in which these cells are entrapped within the iris stroma. Various authors believe that occult trauma is the cause in many, if not all, spontaneous non-pigmented iris cysts.[8 26 27] One report suggests that intrauterine trauma from amniocentesis may be a factor.[28] There was no history of amniocentesis or other prenatal trauma in our cases. Similarly, there was no history or evidence of birth or postnatal trauma.

Immunohistochemical studies with monoclonal antibodies to intracytoplasmic constituents can aid diagnosis of various ophthalmic entities.[29] Immunocytochemical studies of cases 1 and 2 demonstrated a positive reaction only with epithelial cytokeratin markers. These correlate with tonofilaments present at desmosomal junctions. Although this finding substantiates the epithelial origin of the cysts, it does not differentiate between surface ectodermal and neuroectodermal origin.

A recent case report demonstrated hyaluronic acid within epithelial cells of a spontaneous nonpigmented iris cyst.[3] The authors favoured a neuroepithelial origin, since a similar staining characteristic can be obtained from ciliary body epithelium.

Although our four cases had a varied clinical course, they do have certain important features in common. All cases were either diagnosed or showed some iris abnormality within the first two years of life. The diagnosis was made in three of the four cases during general examination or following awareness of a subtle iris anomaly. There was no known history of intrauterine or postnatal trauma in any of the four

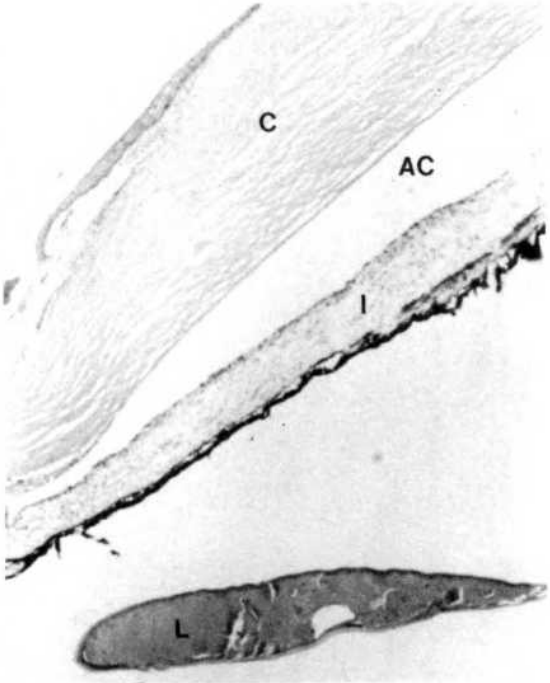

Fig. 12 *(Case 4). Cataractous lens remnants.* C, *cornea;* AC, *anterior chamber;* I, *iris;* L, *lens remnants. Haematoxylin and eosin.*

cases. Three of the four cases had some degree of intraocular inflammation, although it was severe in only one case (4). The clinical course in three of the four cases was characterised by gradual enlargement over years with occasional, mild inflammatory episodes. Treatment was initiated owing to impairment in visual acuity or concern over recent enlargement.

Most reports indicate that iris cysts are not inflammatory in nature and generally produce symptoms only when the visual axis is compromised, but there are earlier reports of uveitis and glaucoma complicating iris cysts.[8] Two of our cases (2 and 3) had mild intraocular inflammation, while one case (4) was associated with episodic severe inflammation. Presumably this resulted from release of mucous or protein debris, causing an inflammatory response and, when severe, blockage of trabecular meshwork. With large cysts a secondary angle closure mechanism may also be contributory.

Several features of case 4 were unusual and deserve comment. The cyst filled much of the anterior chamber, contacting both the corneal endothelium and iris. From histopathological examination only it is not possible to determine if this originated from the iris or from the anterior chamber. The earlier clinical appearance, however, suggested an iris origin. The areas of marked iris stromal loss are presumably secondary to pressure induced ischaemic changes. The presence of cataractous lens remnants is puzzling and suggests possible lens trauma during the paracentesis, though this was not thought to have occurred. There was no history of amniocentesis or other pre- or postnatal trauma.

The occurrence of an orbital dermoid cyst and intraocular epithelial cyst in the same patient is of interest. Dermoid cysts are thought to arise from sequestered surface epithelium.[30] An analogous pathogenic mechanism is likely in the aetiology of iris or anterior chamber non-pigmented epithelial cysts. We are unaware of the simultaneous occurrence of these epithelial cysts in the same patient. Presumably the association here is coincidental.

Several forms of management have been advocated for non-pigmented iris cysts. Congenital iris cysts should be observed for growth if the visual axis is spared. Their characteristic slow growth patterns may allow for prolonged observation and avoidance of operative complications during an amblyogenic age. Of particular interest are reports of spontaneous regression of non-pigmented iris cysts.[31] When the visual axis is compromised, surgical excision remains the most commonly employed treatment. Various forms of excision exist, including sector iridectomy,[2-4 7-10 17 32 33] iridectomy plus corneal curettage,[27] excision plus posterior corneal lamellar resection,[34] iridectomy plus cryotherapy of possible limbal remnants,[33 35 36] iridocyclectomy,[34 37 38] and penetrating keratoplasty plus iridocyclectomy.[39] Recurrences have been reported, including formation of sheet-like epithelial ingrowths.[13 33 36 37 40] These recurrences are most notable in cases of incomplete excision or piecemeal excision as with suction-cutting instruments.[33]

Certain non-excisional treatments have been largely abandoned owing to inherent complications or frequent cyst recurrence, including electrolysis[41 42] and diathermy.[26 43 44] Cyst aspiration with injection of chemicals such as iodine[45] and trichloroacetic acid[46] may be effective, but concern over possible intraocular damage has limited their popularity. Case 3 demonstrates recurrence after trichloroacetic acid instillation.

Photocoagulation with or without cyst aspiration has been used for acquired non-pigmented iris cysts.[37 47-50] However, multiple treatments may be required and recurrences may occur.[37 51] Photocoagulation of congenital iris cysts in children would require use of a photocoagulation device suitable for recumbent patients under general anaesthesia.

We believe that some spontaneous non-pigmented iris cysts are congenital and occur in the absence of trauma. The correct diagnosis is usually established in early childhood. Episodes of intraocular inflammation are frequent. Observation for growth is indicated prior to treatment. The cellular origin is usually, and possibly always, surface epithelium. Developmental entrapment during lens vesicle formation appears to represent a plausible pathogenic mechanism.

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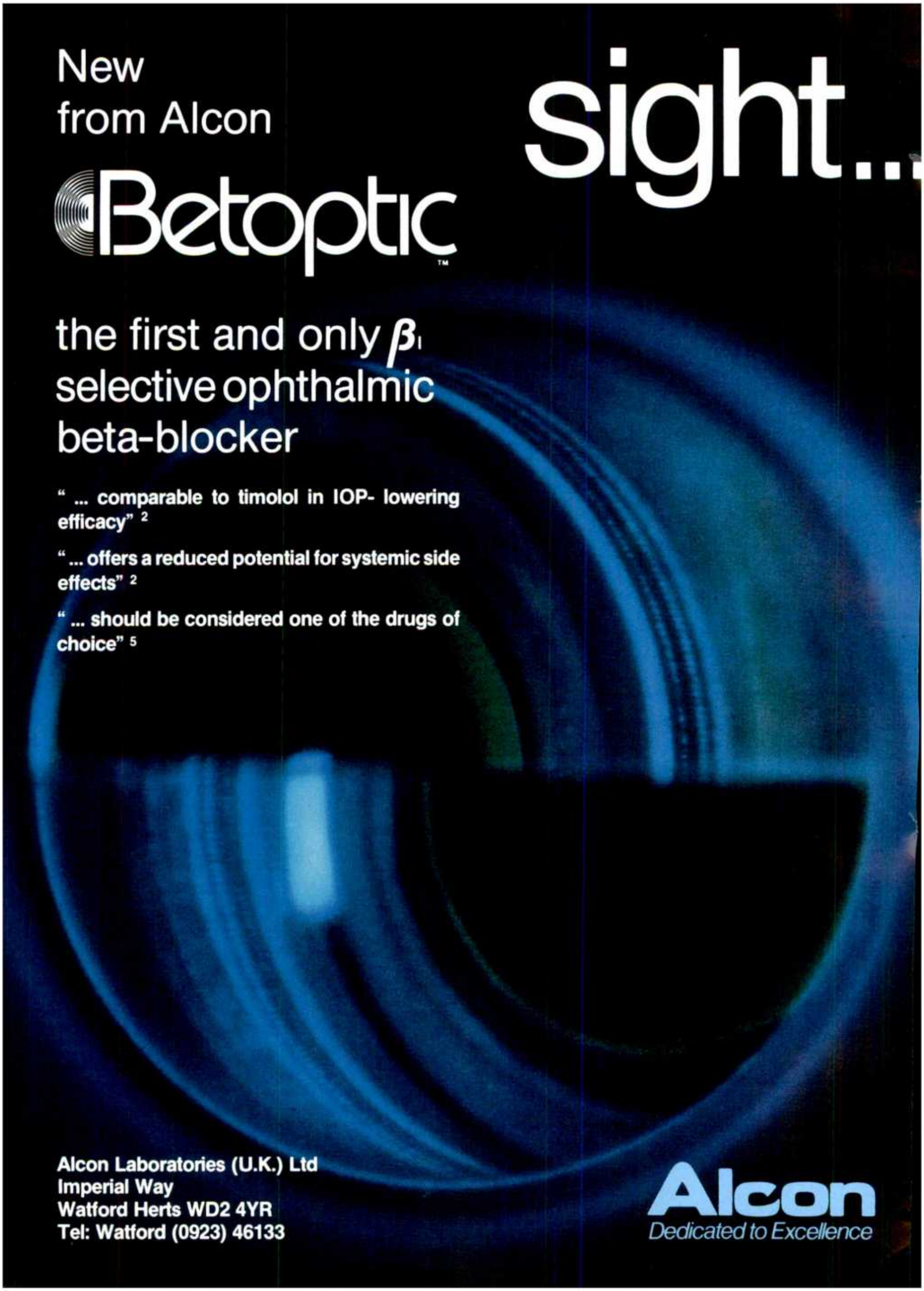

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Ophthalmic manifestations of neurofibromatosis

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SUMMARY The eyes of 64 patients known to have neurofibromatosis were examined. Lisch nodules were the commonest manifestation of the disease and were present in 95% of all patients (100% of those aged 16 years or older).

Neurofibromatosis was first described by von Recklinghausen in 1882.[1] A wide range of complications of the disease are now recognised, and it has become apparent that there are several forms of neurofibromatosis. The one described by von Recklinghausen is by far the most common and is now referred to as von Recklinghausen or peripheral neurofibromatosis. The other forms include central neurofibromatosis, the major defining features of which are bilateral acoustic neuromas with few if any cutaneous manifestations, and segmental neurofibromatosis, where the features of the peripheral form are confined to one segment of the body.[2]

Von Recklinghausen neurofibromatosis (NF) is an autosomal dominant disorder with a high mutation rate and a prevalence of around 30/100 000 of the population.[3] There is no laboratory test for NF and the diagnosis is made on the basis of the major defining features of the disease—café au lait spots and cutaneous neurofibromas. Café au lait spots are flat light brown patches which vary in size from a few millimetres to several centimetres. They begin to develop at or soon after birth and increase in number and size throughout childhood. Some patients with NF also develop axillary freckling, a clinical sign unique to the disease. Cutaneous neurofibromas begin to appear about the time of puberty and increase in number throughout life.

Approximately 25% of patients with NF develop complications which include plexiform neurofibromas, malignancies (of which neurofibrosarcomas and embryonic childhood tumours are the most frequent), scoliosis, congenital bone defects, and tumours of the central nervous system.[4] The complications of NF that may present to the ophthalmologist are optic gliomas, plexiform neurofibromas which involve the orbit, congenital absence of the sphenoid wing, and congenital glaucoma. These are all rare and occur in approximately 5% of patients with NF.[5] Recently, however, Lewis and Riccardi[6] have drawn attention to more frequent but asymptomatic manifestations in the irides of patients with NF.

Abnormalities of the iris in NF were first reported clinically by Waardenburg in 1918,[7] who described small wart-like iris lesion which he presumed to be neurofibromas. Goldstein and Wexler in 1930[8] demonstrated at necropsy multiple melanocytic tumours of the iris in the eyes of a patient with NF. In 1937 Lisch[9] reported three cases of NF all of which had iris nodules. He concluded that they were pathognomic of the disease and that if the irides of more NF patients were examined they would be a frequent finding. The study of Lewis and Riccardi[6] was the first prospective systematic evaluation of the ophthalmological manifestations in a large number of patients with NF.

A prevalence study of NF in South Glamorgan and Gwent has recently been carried out (Huson SM, Compston DAS, Harper PS, in preparation). The principal aim of the study was to look at the variation of the disease in a relatively unbiased population and to re-evaluate the diagnostic criteria. A proportion of the patients in the prevalence study, who had initially been seen at home, attended for ophthalmological assessment at the University Hospital of Wales. We report here our findings, with particular emphasis on Lisch nodules—their incidence in patients with NF and their role in making the diagnosis.

Materials and methods

Patients with NF were ascertained from hospital records, general practitioners, and consultants in the study area. The patients were visited at home (by SH),

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Correspondence to Mr D Jones.

Table 1 *Diagnostic criteria for von Recklinghausen neurofibromatosis*

In children:	≥6 café au lait spots >0·5 cm in diameter
In adults:	(1) ≥6 café au lait spots >1·5 cm in diameter (2) Multiple cutaneous neurofibromas

and a clinical assessment, including portable slit-lamp examination, was carried out on all patients and where possible their first degree relatives. The criteria used for the diagnosis of NF are shown in Table 1.

A proportion of the patients then attended the University Hospital of Wales for more detailed ophthalmological assessment (by LB and DJ). This included: (1) measurement of visual acuity; (2) examination of the periorbita; (3) slit-lamp examination of the cornea and iris (the numbers of Lisch nodules in each eye were counted); (4) direct and indirect ophthalmoscopy.

In patients over the age of 20 years applanation tonometry was performed, and a limited number of patients also had gonioscopy, anterior segment and fundus photography, and fluorescein angiography. As we were particularly interested in the age at which Lisch nodules first develop, a further group of patients (all children) were ascertained through the NF Association, LINK, and their irides only were examined using a portable slit-lamp (Kowa Ltd).

During the study period 150 patients attending the general ophthalmology clinic were also examined for the presence or absence of Lisch nodules.

Results

Fifty-three people with NF attended for hospital assessment, 29 females and 24 males, age range 3–80 years. Eleven children were ascertained via LINK, five females and six males, age range 4–17 years. All the patients were of Caucasian origin. A total of 64 patients were therefore examined for the presence or absence of Lisch nodules. The diagnosis of NF was obvious from facial appearance in only 7/64 (11%) of these patients.

In 95% of the patients (61/64) Lisch nodules were present and were bilateral in 93% (57/61). The age distribution of the patients and number with Lisch nodules in each age group is shown in Fig. 1. The nodules were easily seen in all but one patient, who was aged 9 years and had only two nodules in his right iris. The appearance of the nodules was distinct. They were dome-shaped lesions found on all parts of the surface of the iris, varying in size from being barely visible with the slit lamp to up to 2 millimetres in diameter (Fig. 2). Most of them were brown in colour but a few, particularly in children, were very pale and almost white.

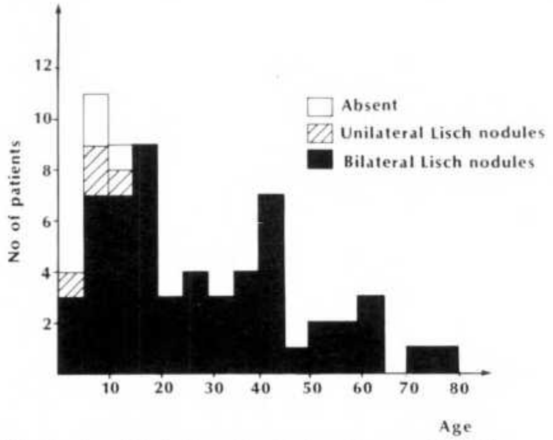

Fig. 1 *Age distribution of patients and proportion with Lisch nodules in each group.*

We were able to count the number of nodules in all but two patients (aged 3 and 4 years). The mean number of nodules per eye was 25 (range 1 to 100). The age of the patient was compared with the mean number of nodules per eye (OS+OD)/2 by the Spearman rank correlation test. There was a highly significant correlation between age and the number of nodules per eye ($r=0{\cdot}404$, $p<0{\cdot}002$). For the patients <16 years ($n=24$) three had no Lisch nodules (13%) and nine (38%) had fewer than 10 nodules per eye, whereas in all patients age ≥16 years

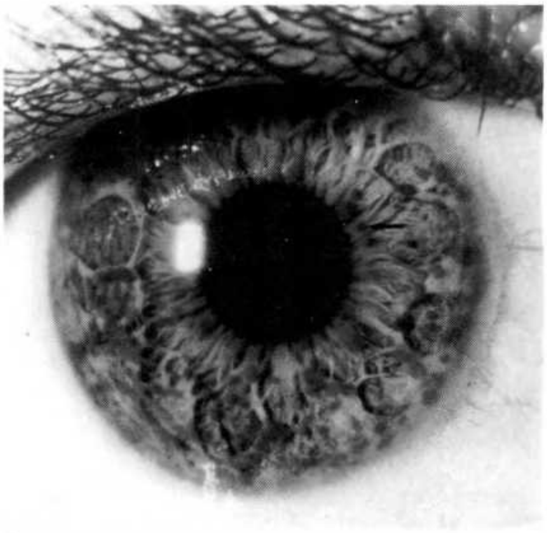

Fig. 2 *Typical appearance of Lisch nodules.*

(n=40) Lisch nodules were present and only 6 had fewer than 10 per eye (15%).

Twenty-one offspring (age range 4 to 39 years) of patients with NF, with no cutaneous manifestations of the disease, were also examined and no Lisch nodules were seen. In addition 150 general ophthalmology outpatients, 76 females and 74 males, age range 8–86 years, were examined. No Lisch nodules were seen in 149 patients. One patient had several iris naevi and two lesions indistinguishable from Lisch nodules on the periphery of one iris. She was 27 years of age and had no family history of NF. The patient and her parents underwent clinical examination. No café au lait spots or cutaneous neurofibromas were present. Slit-lamp examination was normal in both her parents.

The frequency of other ophthalmological findings in the 53 patients ascertained via the population based study is shown in Table 2. The most frequent findings were choroidal 'hamartomas,' which were present in 15/51 (29%), age range 15 to 61 years, and were only easily visible with the indirect ophthalmoscope. They appeared as discrete dark lesions, between 5 and 20 in number, 1 to 2 disc diameters in size, and were scattered around the posterior pole. Fluorography of these lesions (Fig. 3) suggested that they were choroidal naevi.

Discussion

Iris involvement in NF is regarded as rare by some authors.[10 11] In our series of 64 patients with NF Lisch nodules were found in 96% overall and 100% of those aged 16 years or over. We would therefore agree with Lewis and Riccardi[6] that Lisch nodules are the commonest ophthalmic manifestation of the disease and a useful clinical sign. Histologically Lisch nodules have been shown to be melanocytic hamartomas[8 12] and therefore are presumably of neural crest origin embryonically, as are the other major manifestations of NF–café au lait spots and cutaneous neurofibromas.

In their series Lewis and Riccardi[6] found Lisch nodules in 36 (92%) of 39 patients >16 years of age but in only three (23%) of 13 patients <6 years of age. Boltshauser *et al.*[13] have recently reported their findings in 90 patients with NF, 82 (91%) of whom had Lisch nodules. They were present in all the 53 patients aged >16 years but in only 3 (33%) of 9 aged <6 years. In these three series only three patients aged >16 years did not have Lisch nodules. We therefore conclude that over 95% of adults with NF have Lisch nodules and that they begin to develop in early childhood. Both in our series and that of Lewis and Riccardi[6] there was significant correlation between the number of Lisch nodules observed and the age of the patients.

Table 2 *Ophthalmological findings in 53 patients with von Recklinghausen neurofibromatosis*

Lisch nodules	51 (96%)
Choroidal 'hamartomas'	18/51* (35%)
Neurofibromas on eyelids	9 (16%)
Presumed conjunctival neurofibroma	1 (2%)
Prominent corneal nerves	3 (6%)
Glial tissue overlying optic disc	2 (4%)
Bilateral optic atrophy due to optic glioma	1 (2%)

*Only 51/53 patients were examined with an indirect ophthalmoscope.

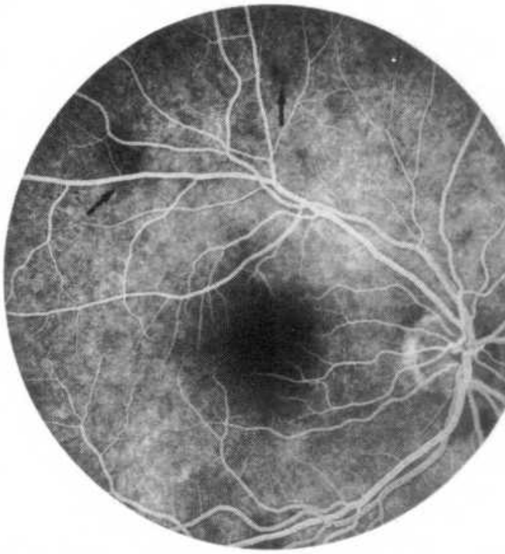

Fig. 3 *Fluorescein angiogram showing the choroidal lesions seen in some patients with NF.*

In the 150 normal subjects we examined only one had two lesions (in the same eye) which were clinically indistinguishable from Lisch nodules. No other features of NF were found in this patient or her parents, neither of whom had Lisch nodules. It may be that this patient has these nodules as her sole manifestation of NF, for which she is a new mutation; we believe this is unlikely. The alternative explanation is that normal individuals may rarely have one or two Lisch nodules but that numbers greater than this are unique to NF. One case has been reported[14] where the only manifestations of NF in the parents of two affected sons were Lisch nodules in the mother. This patient had over 100 nodules in each eye (Riccardi, personal communication).

On slit-lamp examination by oblique illumination Lisch nodules because of their smooth outline and dome-shape are easily distinguishable from iris naevi. We did, however, observe an unusual variation of pigmentation in three patients (two normal subjects and one with NF) which could at first glance be confused with Lisch nodules by the inexperienced observer. These three patients had approximately 100 tiny nodules of dark brown pigmentation confined to the peripupillary region of the iris. The appearance was similar to the mammillations described in some cases of unilateral melanosis by Mann.[15]

Pigmented choroidal lesions were the second most frequent finding and were seen in 18/51 (35%) of the patients. They were best seen with the indirect ophthalmoscope and appeared as discrete areas of hyperpigmentation, dark brown-black in colour, which were flat or only minimally elevated. Fluorescein angiography demonstrated that they were avascular patches of hypofluorescence similar to multiple small choroidal naevi. Lewis and Riccardi[6] found similar choroidal lesions in 51% of their series and referred to them as choroidal hamartomas. Cotlier[16] reported two patients with these lesions and described them as 'café au lait spots' of the fundus, which seems the most appropriate term. None of the patients in this series had either choroidal melanomas or glial hamartomas, and other ophthalmological manifestations of NF were all relatively uncommon (Table 2).

In conclusion, we have found Lisch nodules to be virtually pathognomic of NF. The nodules become manifest in early childhood, are present in over 95% of adults with NF, and are easily seen on slit-lamp examination. They are therefore a useful clinical sign and under appropriate circumstances can be used to establish or exclude the diagnosis of NF. If a child with multiple café au lait spots is found to have Lisch nodules, then the diagnosis is confirmed. Conversely, if the children of a patient with NF reach the age of 5 years and have neither café au lait spots nor Lisch nodules, it is extremely unlikely they have inherited the disease.

Most clinicians perceive patients with NF as having the severe form of the disease, but in the majority of patients the diagnosis is not obvious at first glance (89% in this series). Similarly many patients are unaware of the disease complications and therefore do not think it relevant to mention their NF when attending an ophthalmology clinic. The finding of Lisch nodules on slit-lamp examination should alert the ophthalmologist to the diagnosis of NF and the consideration that the patient's presenting symptoms may be due to one of the complications of the disease.

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Topical steroid, cyclosporin A, and the outcome of rat corneal allografts

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SUMMARY The effects of a combination of topical corticosteroid and cyclosporin A on corneal graft survival were tested in a model of penetrating keratoplasty in the inbred rat. Topical medications were applied four times daily to the graft for 28 days postgraft. Neither topical steroid (1% prednisolone acetate) nor topical cyclosporin (1% in chremophor EL/ethanol) was able to modify the overall incidence of rejection, though all steroid-containing medications delayed the onset of rejection significantly. The combined formulation of steroid plus cyclosporin A caused a reduction in the incidence of rejection which did not reach statistical significance and which did not eliminate the response in all animals. The chremophor/ethanol vehicle was reasonably well tolerated but did cause some periocular dermatitis.

Despite intensive treatment with topical corticosteroids many corneal grafts performed in patients with pre-existing corneal vascularisation or a history of anterior segment inflammation will fail from rejection.[1] Because blindness is not a life-threatening disorder, the risks of morbidity and death associated with the systemic administration of non-specific immunosuppressive agents are seldom considered to be justifiable in corneal transplantation. Topical steroid is a relatively safe and effective immunosuppressive drug for corneal transplantation in the subgroup of patients with diseased but avascular, non-inflamed corneas. However, when the recipient cornea is vascularised, or the eye inflamed at the time of surgery, maximal doses of topical corticosteroid will not always prevent rejection. There is clearly a need, therefore, for an improved regimen of topical immunosuppression for high-risk patients with vascularised and inflamed eyes.

Topical cyclosporin A has been shown to prolong the outcome of corneal grafts in the rabbit,[2,3] but a comparative study of the effects of short-term topical steroid and cyclosporin A in a rabbit model in which the recipient cornea was vascularised and inflamed showed that the conventional treatment, topical steroid, was more effective than cyclosporin A in prolonging corneal graft survival.[4] Furthermore, Mannis and May reported similar findings when comparing topical steroids with cyclosporin A administered by retrobulbar injection.[5] However, the possibility that a combination of the two drugs might be more effective than either one or the other has not yet been examined. We have therefore tested the effects of short-term, topical administration of steroid, cyclosporin A, and a combination of the two in a model of penetrating keratoplasty in the inbred rat. Because of problems previously encountered by us and by others in the use of oily vehicles for topical administration of cyclosporin A to the rabbit eye,[3,4] we elected to test an alternative vehicle, 70% chremophor EL/30% ethanol. This has previously been reported by Wiederholt and his associates to be well tolerated by the rabbit.[6]

Material and methods

Animals. Female 12-week-old Fisher 344 and DA rats were used as recipients and donors, respectively.

Topical medications. Prednisolone acetate, 1% w/v (Prednefrin Forte) was chosen as the topical corticosteroid because this formulation is frequently used in clinical practice. Cyclosporin A (Sandoz) was dissolved in a vehicle of 70% v/v chremophor EL (BASF)/30% v/v ethanol and filtered through a 0·22 μm Millipore membrane before use. A combined formulation was prepared by mixing the steroid and cyclosporin A solutions to yield a 0·5% v/v preparation of each. Medications were

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routinely stored at 4°C but were warmed to ambient temperature and shaken vigorously before use.

Rat corneal grafts. Penetrating grafts 3 mm diameter were performed in prevascularised eyes as previously described.[7] Graft sutures were not removed postoperatively.

Treatment protocol. Five experimental groups were set up, each containing 10-15 recipients: no treatment, treatment with chremophor EL/ethanol vehicle, steroid, cyclosporin A in vehicle, and the combined preparation. One drop of the appropriate medication was applied to the graft in the immediate postoperative period and then four times daily for 28 days postgraft. Animals were killed at day 60 postgraft.

Graft assessment. Grafts were examined under the operating microscope at 24 hours and three times weekly thereafter. The observer was unaware of the treatment applied to the rats being scored. Grafts were scored on a 0-3 scale for oedema, clarity, inflammation, and vascularisation, with 0 representing a perfect graft, that is, a non-oedematous, perfectly clear graft in an uninflamed eye, with no vessels (or ghost vessels only) crossing the host-graft margin. A score of 3 represented a thick, opaque graft, heavily vascularised, in an inflamed eye.

Histology. All grafts were taken for endpoint histological examination. Kidney and liver were also removed from some animals. Buffered formalin-fixed tissue was embedded in JB4 resin and 2 μm thick sections were stained with haematoxylin and eosin.

Results

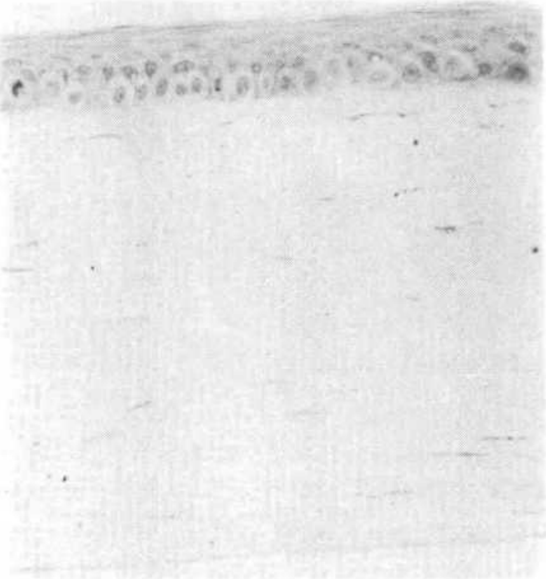

Fig 1 *Histological section of rat corneal isograft from animal treated with chremophor EL/ethanol.*

Acceptability of the chremophor EL/ethanol vehicle in the rat eye was tested in a pilot experiment, in which rats bearing corneal isografts were treated four times daily for 28 days postgraft. The vehicle was quite well tolerated, and endpoint histology of the grafts was unremarkable (Fig. 1).

The outcome of corneal allografts in the five experimental groups is presented in Table 1. Approximately 80% of control allografts underwent an episode of graft opacification (usually partial) with oedema, inflammation, and neovascularisation, considered to reflect rejection. Graft scores for these rejected corneas ranged from 1 to 3.

None of the three regimens of drug treatment tested was able to modify the overall incidence of rejection to a significant extent. The combination of topical steroid plus cyclosporin A caused a reduction in the incidence of rejection that reached significance

Table 1 *Incidence of rejection, median day to rejection, and weight gain between end of treatment period and end of observation period in rats with corneal allografts: effect of various regimens of topical immunosuppression*

Group	*Topical medication*	*Number*	*Number with rejection episode*	*Median day to rejection*		*Weight increase (g), day 28–60 postgraft, mean ± SD*
				All rats	*Excluding non-rejected grafts*	
1	No treatment	15	13	8	7	14 ± 6
2	Chremophor/EL ethanol	15	11	7	6	13 ± 5
3	1% steroid	9	6	15*	12†	38 ± 9‡
4	1% cyclosporin A	13	12	7	7	10 ± 5
5	Combination of 0·5% steroid plus 0·5% cyclosporin A	11	5	60*	9†	39 ± 12‡

* $p<0{\cdot}01$ cf groups 1 and 2
† $p<0{\cdot}05$ cf groups 1 and 2
‡ $p<0{\cdot}001$ cf groups 1, 2 and 4

at the 5% level (Fisher's exact test, one-tailed) when compared with the no-treatment control group ($p=0{\cdot}034$) or the combined control groups (groups 1 plus 2, $p=0{\cdot}036$), but not when compared with the group receiving vehicle alone.

Both topical steroid and the combination of topical steroid and topical cyclosporin A were able to delay the onset of rejection to a significant extent when compared with either of the control groups or the cyclosporin A group (Mann-Whitney U test). The combined formulation appeared significantly better than steroid alone when all grafted animals were considered ($p<0{\cdot}02$, two-tailed), because the combination increased the proportion of animals not undergoing a rejection episode during the period of observation. When the latter group was excluded from the analysis, the combined medication was no better than the topical steroid.

Of the 78 rats grafted 15 were judged to be technical failures (four infections, four cataracts, three early anaesthetic deaths, and four poorly sutured grafts) and were excluded from all analyses. Infections and cataract formation were approximately evenly distributed over all groups.

An unexpected observation was that animals treated with steroid, either alone or in combination with cyclosporin A, became anorexic and failed to thrive. The weights of these rats were significantly lower than those of animals in any other group (*t* test, $p<0{\cdot}01$) at 28 days postgraft. Once medication was stopped, however, all animals in the two groups that had received steroid rapidly gained weight (Table 1), so that by 60 days postgraft there was no significant difference in mean weights among rats in any of the five groups.

Endpoint histological examination of all grafts was unremarkable. No evidence of nephrotoxicity or hepatotoxicity was found in sections of kidney and liver removed from a proportion of the animals that had received cyclosporin A.

Discussion

A major difficulty in the examination of factors affecting experimental corneal graft rejection lies with the absence of an entirely appropriate experimental model. Rabbit models are cumbersome, first-set corneal graft rejection can be induced reliably only if the recipient eye is prevascularised or an eccentric graft is performed, and inbred strains are not widely available. The vascularised inbred rat eye provides an alternative model, but is also less than ideal in that only 75% of animals in a strongly histoincompatible combination will undergo corneal graft rejection. Furthermore, rat endothelium has the capacity for extensive regeneration by mitosis as well as by cell enlargement and sliding,[8] unlike human endothelium, in which the regenerative capacity is very low.[9] Rabbit endothelium can also undergo mitosis,[10] but an intact monolayer is more quickly re-established across a denuded rat cornea, probably because of the smaller size of the eye. Final graft outcome is thus an insensitive endpoint in the rat, and the incidence of rejection needs to be examined instead.

None of the regimens of topical medications tested was successful in abolishing corneal graft rejection in our model, despite the relatively high doses of drugs that were applied to the eye (approximately 10 mg/kg/day, based on a drop volume of 25 μl). The combination of steroid and cyclosporin A significantly reduced the incidence of rejection compared with the use of either drug alone, but the biological effect was marginal, with 45% of animals receiving the combined medication still undergoing an episode of rejection.

Topical steroid had no significanct effect on the incidence of corneal graft rejection in this model, in contrast to the findings in the rabbit, where topical steroid is most effective.[4] However, rat corneal grafts treated with topical steroid (either alone or in combination with cyclosporin A) were less inflamed and less vascularised than grafts in other treatment groups. The model may thus reflect the situation in high-risk clinical cases with fair accuracy.

The choice of the best vehicle in which to dissolve a topical formulation of cyclosporine for experimental studies remains a problem. Previous studies have generally specified olive or arachis oil, but there is inevitable variation among different batches of these oils and both can act as ocular irritants.[2 4 11] The combination of chremophor EL/ethanol used in this work was tolerated remarkably well in the rat eye, with no obvious toxicity evident, but periocular dermatitis observed in previous studies with olive and arachis oils was again experienced with this vehicle.

The actual route and extent of absorption of medication applied topically to the eye in experimental animals deserve further attention. It was observed over the course of these experiments that the rats almost always rubbed their eyes and then licked their paws after a drop of any sort was applied to the grafted eye. Some of the formulations may thus have been absorbed orally, and in any event limited oral absorption might well be expected for any drug applied topically to the tear film because of overflow through the normal lacrimal drainage channels. The unexpected failure of steroid treated rats to gain weight while undergoing topical treatment may conceivably have reflected some oral absorption.

Within the constraints of the model our data indicate that a combination of topical cyclosporin A and steroid is unlikely to provide a significant therapeutic advance over topical steroid alone, the current mainstay of immunosuppression for corneal transplantation.

We thank N Robson and A Neville for technical assistance, E Andrea and W Laffer for editorial assistance.

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Book reviews

Walsh and Hoyt's Clinical Neuro-Ophthalmology. 4th edn. Vol. 2. By NEIL R MILLER. Pp. 1133. £76·00. Williams and Wilkins: Baltimore. 1985.

The second volume of the fourth edition of this book is welcome. The first volume covered the visual sensory system and the optic nerve, and the present volume comprises three sections. These are on the autonomic nervous system, the ocular motor system, and sensory innervation of the eye and the orbit.

The section on the pupil is extensive (270 pages), informative, and superbly illustrated. The clinical section has not altered in substance since the previous edition, though the bibliography is brought up to date, and the authoritative eyes of Lowenfeld and Thompson have cast their sign of approval. The pupil remains of interest and of clinical importance to the ophthalmologist. Thus Horner's syndrome is extensively covered, and its relevance to ophthalmologists is emphasised by the fact that a preganglionic Horner's syndrome carries a mortality of 55%. The afferent pupillary defect and the tonic pupil are also fully considered. On the anatomical side the illustrations are exquisite; some are culled from Hogan and Alvorado, others are either original or from recent papers. The illustrations of sprouting after axonal injury are impressive, and the appearances they show may be visualised within 24 hours of nerve injury.

The ocular motor system (inappropriately referred to as the oculomotor system on the page headings) has been written with the collaboration of Dr David Zee. The opening chapter on embryology and anatomy contains remarkable diagrams and electron micrographs. The neural control of eye movements has been an area of 'shifting' interpretation over the past decade, as the new microrecording techniques have rewritten conventional connections.

Similarly the use of retrograde tracing techniques—namely, horseradish peroxidase, wheat germ agglutinin—have shown how complex neural connections can be. Thus Warwick elaborated third nerve nuclear organisation using degenerative techniques, but injection of tracers into the medial rectus, for example, has shown three different subgroups in the ipsilateral nucleus, which might indicate different areas for adduction and convergence control. The clinical evaluation of ocular movement disorders remains largely unchanged, though emphasis has been placed on the value of the vestibulo-ocular reflex (VOR). In addition useful sections on Duane's syndrome and other congenital innervational disorders are well described. This section is a mammoth task and includes a bibliography of over 1400 references. The final chapters on ocular muscle disorders and nystagmus are again comprehensive and update ophthalmologists on the biochemical nature of ocular myopathy (PEEO) and the current immunology of myasthenia gravis.

The section on the trigeminal nerve is extensive enough to grace the pages of any textbook of neurology. The subject is of interest to ophthalmologists, though large sections on glossopharyngeal neuralgia and the Ramsay Hunt syndrome seem to widen rather unnecessarily the diagnostic horizons of clinical neuro-ophthalmology.

This volume therefore follows the pattern of its predecessor in providing an up-to-date review, supported by ample and excellent illustrations and the most extensive bibiliography. The aim of the book has been altered, to provide the 'ultimate reference book' rather than the 'ultimate clinical opinion'. An ophthalmologist's library would be a sadder place without these volumes, and the author is to be congratulated on his amazing achievement. M D SANDERS

The Interphotoreceptor Matrix in Health and Disease. Eds. C. DAVID BRIDGES AND ALICE J. ADLER. Pp. 287. £37·00. Alan R. Liss: New York. 1985.

Who would have thought a few short years ago that the glycoprotein matrix surrounding the outermost components of the photoreceptor cells would find itself the subject of an entire book. Until relatively recently the interphotoreceptor matrix was almost ignored, and there were even those who did not believe it existed. In this book we find not only that it exists but that it may well have profound implications in the study of the pathobiology of retinal disease.

David Bridges and Alice Alder have done the ophthalmic and vision research community a great service in commissioning the authors whom they have persuaded to write so expertly in each part of this book. But their contribution extends further, in that they have obviously paid much attention to the way in which the volume is laid out and also to sustaining logic and concepts between the contributions of the individual authors.

The book is arranged in two parts with the first being further subdivided. Part 1 deals with the normal function of the interphotoreceptor matrix and is subdivided into two sections, the first covering morphology and the second biochemistry and cell biology. The second and final part of the book deals with various parameters of the diseased state. In dipping into the volume therefore we are given a historical review of the early years and debates on the interphotoreceptor matrix by Lynette Feeney-Burns. Hers is a delightful chapter and one which covers many of the misconceptions in relation to this extracellular system. We are then taken through the modern concepts of morphology of the interphotoreceptor matrix as revealed by rapid freezing techniques. The morphological section concludes by highlighting the heterogeneous nature of this system in relation to specialisations juxtaposed to cone photoreceptor cells. The normal biochemistry and cell biology are introduced by an extremely useful review of the matrix by Elaine Berman. Her colleagues then become progressively more and more specialised, explaining such complexities as specific phosphodiesterases in the matrix and the importance of interstitial retinol binding proteins in this region.

After reviewing the normal aspects of this tissue the authors give us a mechanistic review of the various potentials of faults in this system in relation to photoreceptor cell diseases. In a series of chapters the role of specific chemical subcomponents in the matrix in relation to inherited retinal diseases are highlighted and a number of examples are given.

I found this book an absolutely delightful volume and one that was extremely hard to put down. It is short enough to be read in just a few sittings and unlike most specialist texts this is not one the reader should dip into selectively. It is a model of clarity and to my mind a superb example of what every multiauthor work should strive to be. I thoroughly recommend it to all with an interest in the underlying aetiology of retinal diseases. JOHN MARSHALL

Manual of Ocular Diagnosis and Therapy. 2nd Edn. Edited by DEBORAH PAVAN-LANGSTON. Pp. 494. US $17·95. Little, Brown: Boston, Mass. 1985.

The second edition of this book is welcome as an updated version of a ready reference manual. Although the preface claims it is written for a wide readership, it can be used effectively only by established ophthalmologists and residents in ophthalmology, as considerable clinical knowledge in ophthalmology is an essential prerequisite. There are 15 short chapters written by a panel of 11 ophthalmologists and one neurologist mainly from the Boston hospitals and Harvard Medical School, USA.

The standard selection of chapters covers the field of ophthalmology and neuro-ophthalmology. Clear headings and a concise text are an excellent feature of this manual, though there are very few illustrations indeed, and all black-and-white diagrams. Hence previous clinical knowledge in ophthalmology is essential for the readership. The comprehensive lists of causes and differential diagnosis are very helpful, especially to residents taking examinations and thinking widely on a topic. Established ophthalmologists will find these lists valuable also, making sure they have not forgotten any aspect of a patient's investigations. The lists in chapter 14 of ocular manifestations of systemic disease are comprehensive, and the appendixes A and B on common dosages of ophthalmic drugs and antibiotic dosages and routes of administration are especially useful.

The manual is published in soft cover with a spiral binding and may be regarded as an excellent and convenient ready reference book for ophthalmologists and particularly those engaged in postgraduate teaching. The editor and the panel of writers have provided a remarkably concise and comprehensive addition to postgraduate ophthalmic literature. JAMES L KENNERLEY BANKES

Notes

OSUK Annual Congress

The Annual Congress of the Ophthalmological Society of the United Kingdom will be held on 8-10 April 1987 at St David's Hall, Cardiff. Applications to present free papers are invited. Details from Mr Z J Gregor, FRCS, Honorary Secretary, Ophthalmological Society of the United Kingdom, 35-43 Lincoln's Inn Fields, London WC2A 3PN.

Multiple sclerosis

A conference will be held on 3-5 September 1987, at Lyon, France, on 'Trends in European multiple sclerosis research' by the Congress of the European Committee for Therapeutic Research in Multiple Sclerosis (ECTRIMS). Further information from Dr C Confavreux, Hôpital Neurologique, 59 Boulevard Pinel, 69003, Lyon, France.

IX International Course of Ophthalmology

This will be held at Barcelona on 24-29 May 1987. Details from Instituto Barraquer, Laforja 88, E-08021 Barcelona, Spain.

Epidemiology and biostatistics

The National Eye Institute of America will hold a Clinical Vision Research course on 'Epidemiologic and Biostatistical Approaches' at Longboat Key, near Sarasota, Florida, on 29 April to 2 May 1987. Details from Catherine M Beinhauer, Conference Management Associates Inc., 127 Brook Hollow, New Hampshire 03755, USA.

British Contact Lens Association

Applications are invited for the 1987 Dallos Award, whose object is to support contact lens orientated research. Applications will be accepted only from paid up members of the BCLA. Further details from the association's General Secretary, 14 Perceval Avenue, London NW3 4PY.

Talking newspapers

Tape recordings from daily newspapers and weekly and monthly magazines are available on tapes playable in ordinary tape players. For £5 the subscriber receives a 90-minute tape every week for a year. No postage is required if the subscriber is a registered blind person. Details from Talking Newspaper Association of the UK, 90 High Street, Heathfield, East Sussex TN21 8JD.

Correction

In the article by L P Fong, C J Hunt, M J Taylor, and D E Pegg on 'Cryopreservation of rabbit corneas: assessment by microscopy and transplantation' (*Br J Ophthalmol* 1986; **70:** 751-60) an error occurred in the second paragraph (page 751). The last three sentences of it should read as follows: 'A similar solution has been proposed for cryopreservation of the cornea.[13 14] It contains the buffer N-tris (hydroxymethyl)-methyl-2-aminoethane sulphonic acid (TES) and is designated CPTES. Specular microscopy has been used to demonstrate that rabbit corneas will tolerate the introduction and removal of 1 and 2 molar Me_2SO in this solution at 0°C.' We greatly regret this error, which was due to the transposition of two lines of type.

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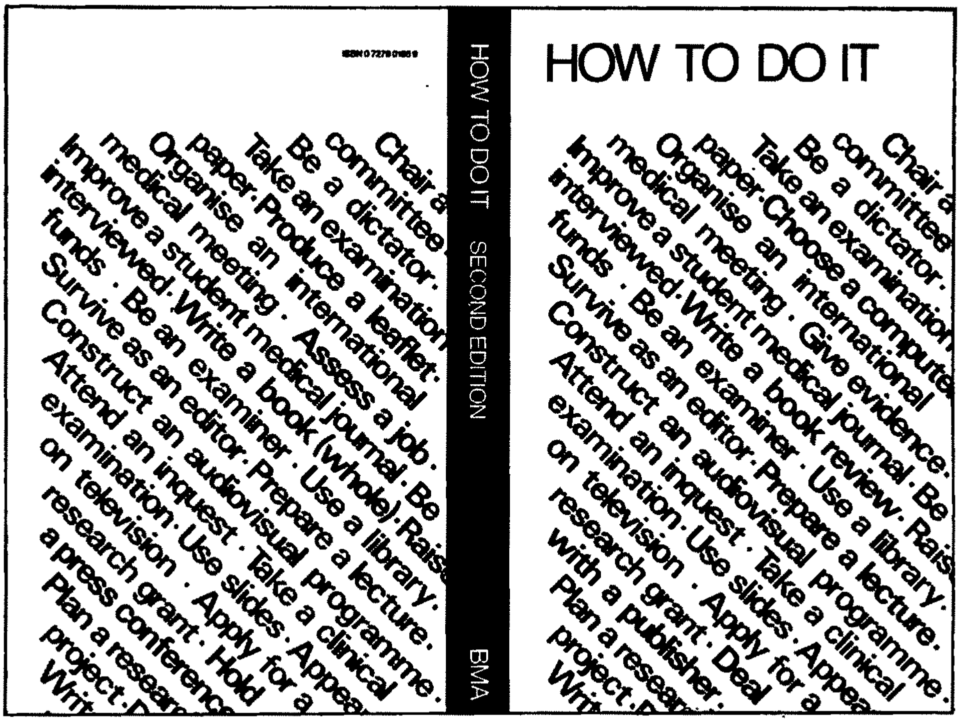
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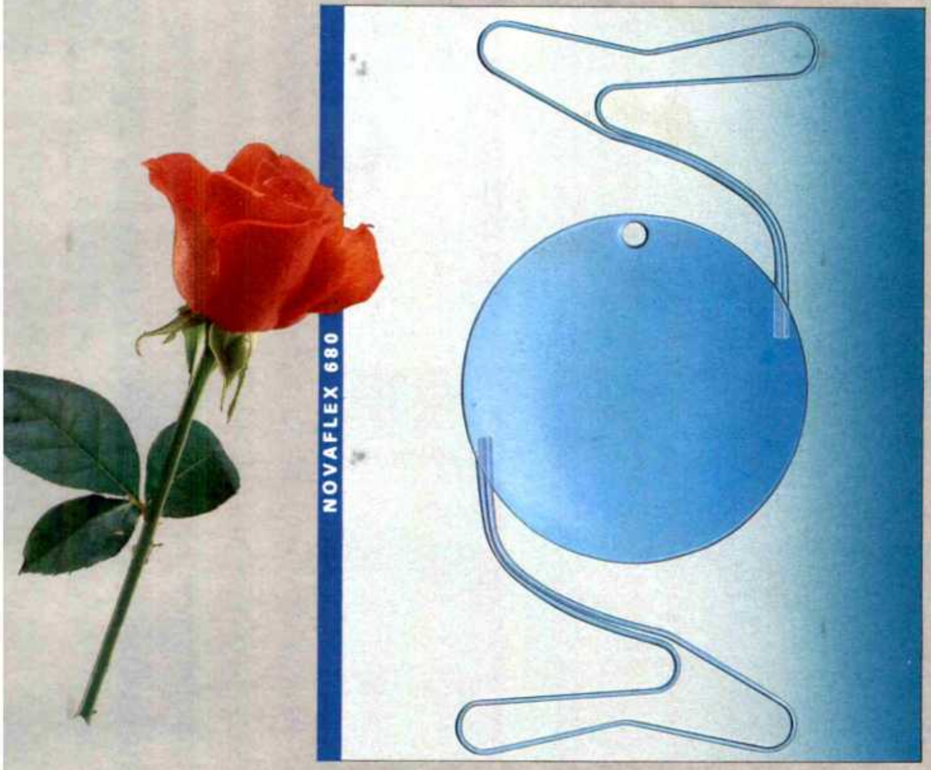

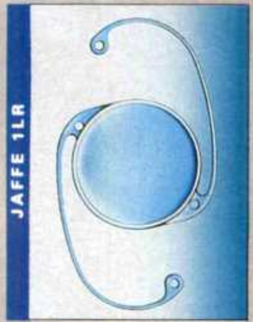

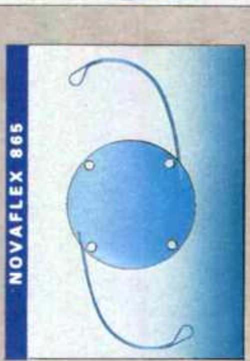

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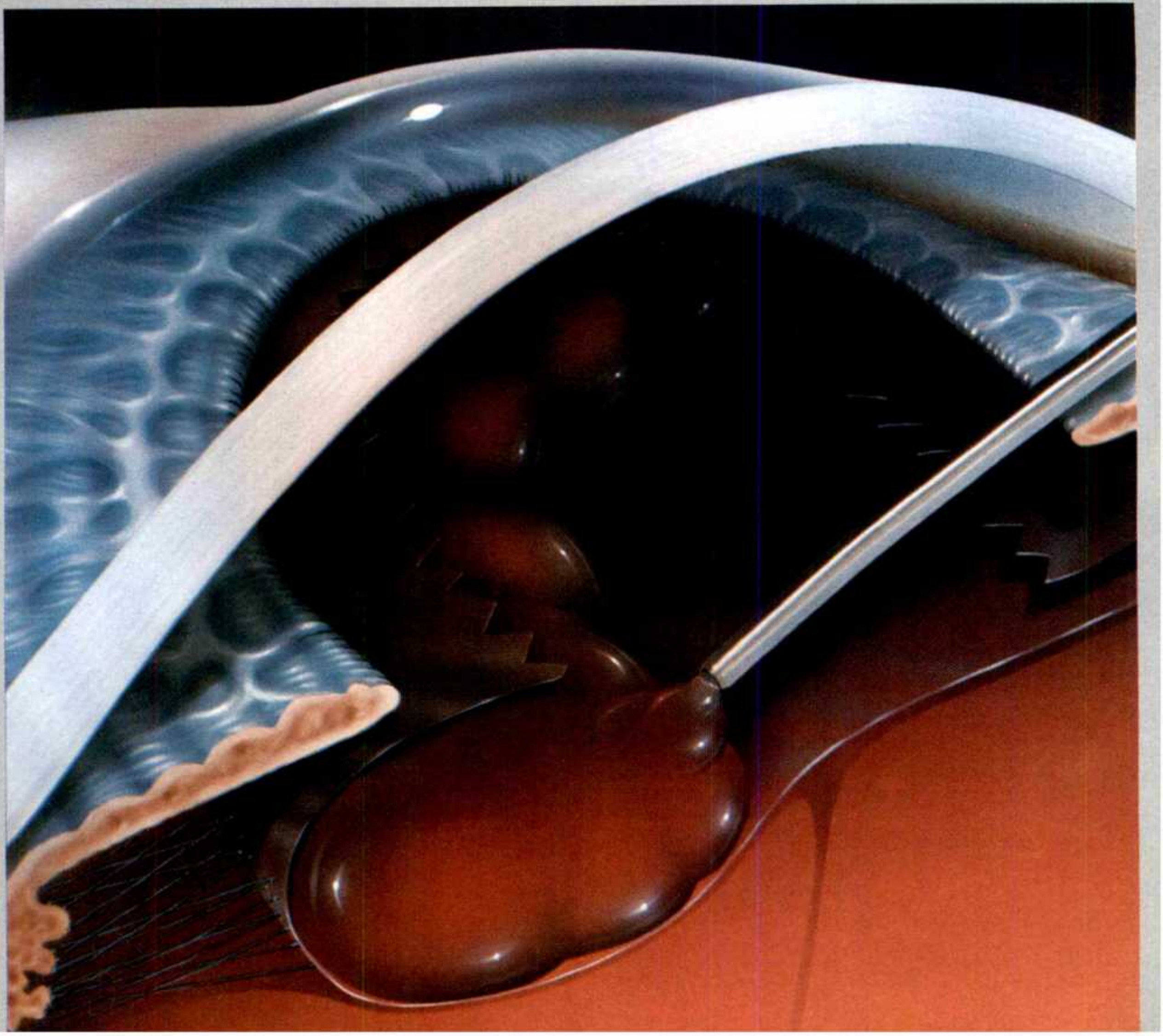

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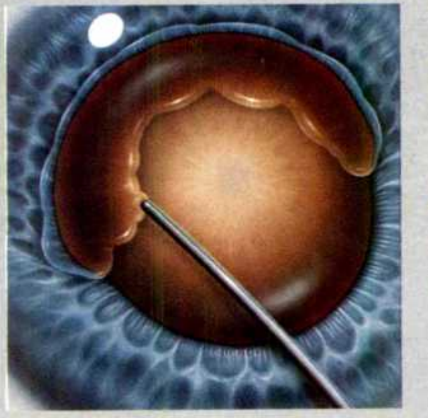

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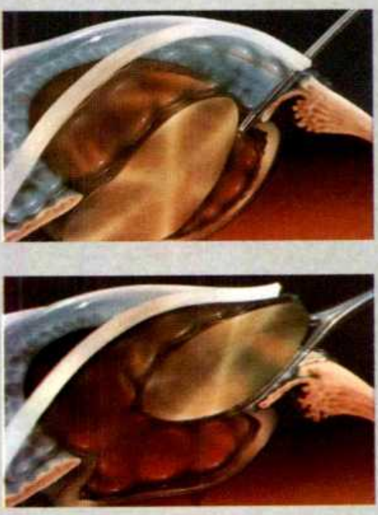

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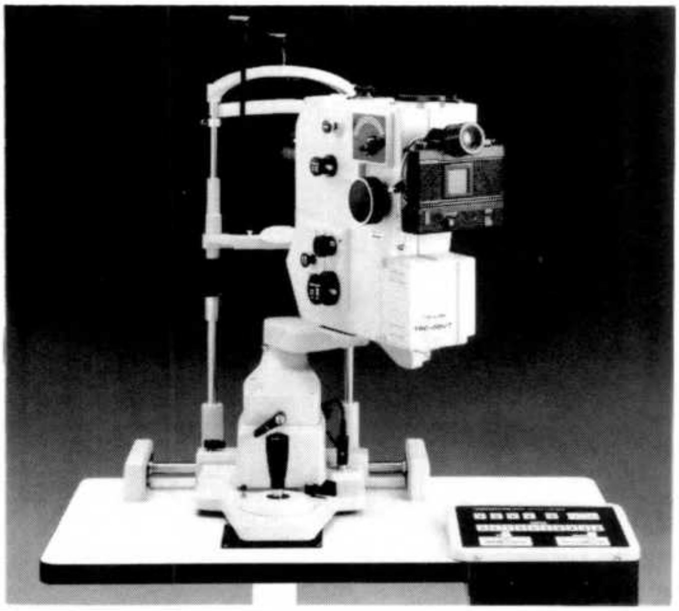

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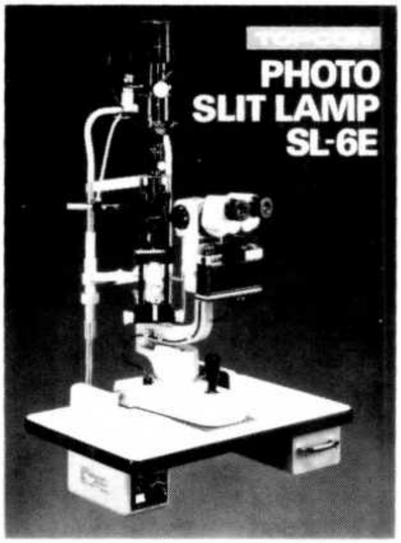

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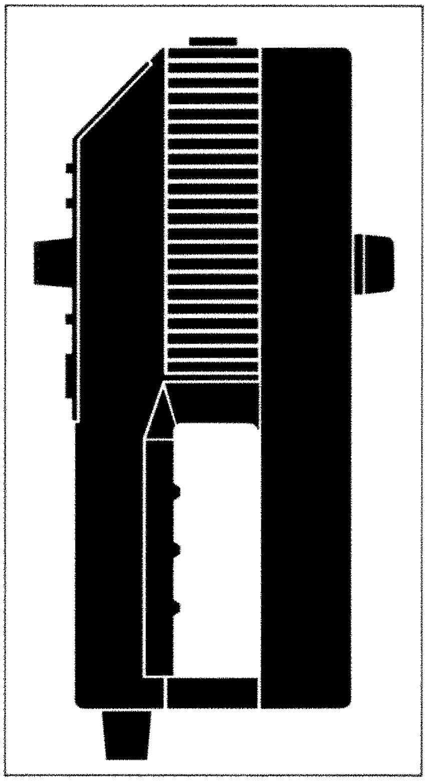

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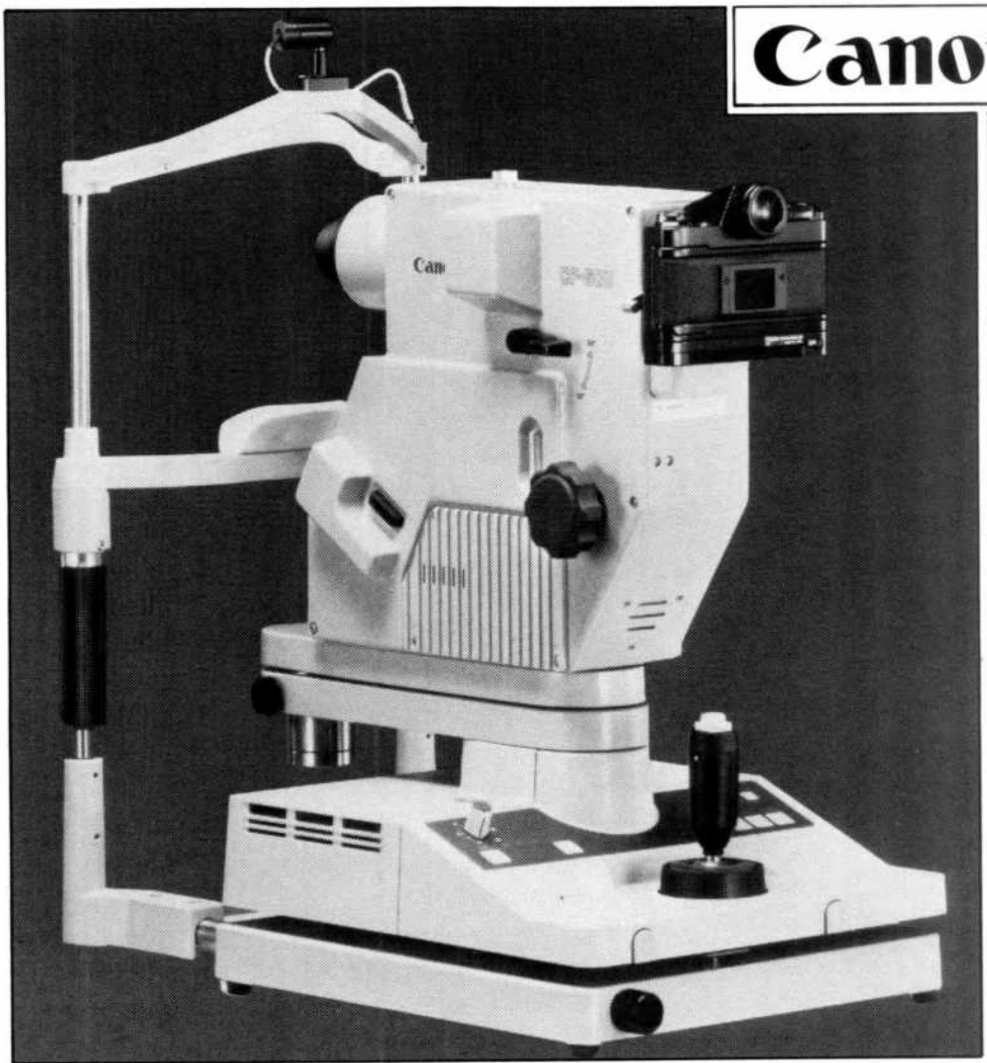

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British Journal of Ophthalmology, 1987, **71**, 245–249

Intraocular pressure, systemic blood pressure, and age: a correlational study

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SUMMARY An attempt was made to study the associations between age, intraocular pressure, and systolic blood pressure. The eyes of 90 non-glaucomatous, ocular normotensive patients and of 142 ocular hypertensive patients were examined. A third group was formed from these two by stratification, to mirror the intraocular pressure distribution in the general population. In all three groups systolic blood pressure was positively correlated with age. In the stratified group a 'chain' model was consistent with the data. Intraocular pressure was significantly negatively correlated with systolic blood pressure; any apparent association between intraocular pressure and age was fully accounted for through the correlation between systolic blood pressure and age.

The relationship between intraocular pressure, age, and various cardiovascular risk variables is not fully understood. The most significantly correlated triad appears to be intraocular pressure, age, and blood pressure, but the associations between these three variables have been inconsistently reported.

Several univariate studies seem to indicate significant positive correlations between intraocular pressure (IOP) and age, and IOP and blood pressure (BP).[1-3] Klein and Klein[1] refer to the possible interference of age as it affects the association they observe between IOP and BP.

Leske and Podgor[4] examined 2315 eyes and carried out a stepwise regression of IOP on a large carrier set, including age, sex, height, systolic and diastolic BP, diabetes, ventricular rate, and vertical and horizontal cup/disc ratio. They found a positive correlation of IOP with systolic BP ($R^2=3\%$); with other, less significant variables added to the regression, the final R^2 reached 5·8%. Age was found not to be significant once systolic BP had entered the regression. They also made the interesting observation that IOP and systolic BP seemed to be correlated only in eyes with glaucomatous visual defects; moreover, the ratio of systolic BP to IOP was significantly lower in eyes which had such defects. They suggested that the non-significance of age may be attributable to the hypothesis that, after controlling for BP, the age effect on IOP may be present only in younger persons. They further raised the possibility that raised systemic pressure may precede raised IOP in a given patient, but did not test this with their cross-sectional data.

Shiose *et al.*[5,6] examined 127 842 eyes. Univariate regressions indicated a negative correlation of IOP with age, a positive correlation with body weight, and a positive correlation with BP. They performed a stepwise regression of IOP on a carrier set containing BP, age, weight, calcium, packed cell volume, haemoglobin, glucose tolerance, alkaline phosphatase, and other variables, and obtained a regression with positive coefficients on weight and BP and a negative coefficient on age, yielding $R^2=4{\cdot}8\%$. They attempted to explain the negative correlation with age by suggesting that the Japanese population tends to be less hypertensive and less obese with age than Caucasian populations, which report a positive age correlation. This explanation may not, however, be sufficient, since the partial regression coefficients in a multiple regression equation are adjusted for the presence of the other covariates in the equation. In a recent study by Daoping Lu *et al.*[7] on 155 eyes followed for a five-year period, a significant positive correlation between systolic BP and IOP ($R^2=15{\cdot}7\%$) was found only in progressing cases of glaucoma.

The present study was undertaken with the aim of combining the use of regression and of path

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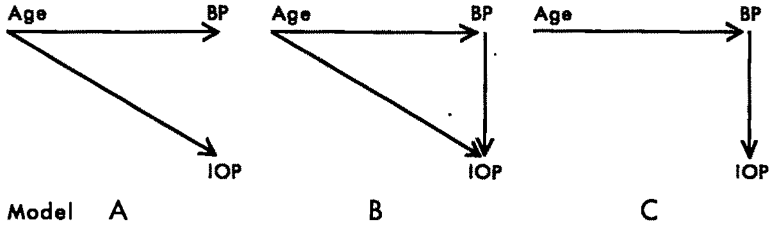

Fig. 1 *Hypothetical schematic models for the age/BP/IOP relationships.* A: *BP/IOP independence.* B: *All pairs correlated.* C: *Age/IOP conditionally independent, given BP.*

analysis[8-11] in order to elucidate the associations among the three variables, IOP, BP, and age. Three models were examined (Fig. 1). Model A allowed for independent age effects on both BP and IOP, model B considered pairwise interactions for all pairs of variables (age and BP, age and IOP, BP and IOP), and model C, a chain model, allowed only for age effect on BP and for a direct BP effect on IOP. It may be recalled that the chain model was recognised by Galton[12] in the 19th century, when he pointed out that, if the sole 'cause' of correlation between the traits i and j was a third trait g, then the relationship

$$r_{ij} = r_{ig}\, r_{jg}$$

must hold between the pairwise correlation coefficients. This was later validated by Spearman[13 14] in his characterisation of 'general intelligence', and it was ultimately seen to be equivalent to a zero partial correlation coefficient.

Materials and methods

The sample consisted of 90 normal patients and 142 patients with ocular hypertension. These patients were fully described in our previous work[15 16] on the use of discriminant analysis in predicting glaucomatous visual field damage. The normal sample was selected to be in the same age group as our regular run of glaucoma patients, and our approach was to encourage the spouses of glaucoma patients to volunteer for the normal study. Normal patients had a full ocular examination including ophthalmodynamometry, gonioscopy, stereoexamination of the optic nerve heads; systemic blood pressures were measured and a full history taken. A neurovascular examination was carried out, excluding invasive procedures unless these were clinically indicated from a neurological standpoint. *X*-rays of the sella and optic foramina excluded those patients with obvious space occupying lesions. Laboratory tests included electrocardiography, 2-hour post-cibum blood glucose, blood urea nitrogen, uric acid concentrations, ESR, haemoglobin level, serum cholesterol and triglycerides, and a T4 test for thyroid function. The visual field had to be normal when examined by Armaly's selective perimetry[17] method as modified by us[18] on the Goldmann perimeter. Intraocular pressures checked on at least two occasions had to be below 21 mmHg.

The ocular hypertensive group consisted of consecutive patients with repeated applanation pressures above 21 mmHg in at least one eye, having normal visual fields, examined in the same way, and with normal optic nerve heads on stereo-ophthalmoscopy.

The associations among the three variables, age, BP, and IOP, were examined within the normal and the ocular hypertensive groups. In addition a stratified group was formed from these two to represent a general non-glaucomatous population (93% normal pressures, 7% ocular hypertensives), by adding a random selection of seven patients from the ocular hypertensive group to the 90 normal persons. The relationships between the variables were explored separately in the stratified group.

In an attempt to investigate these relations univariate regressions were first calculated between each pair of variables. In addition, multiple regressions of IOP on age and BP were calculated. Following the techniques of simultaneous regressions and path analysis[9-11] an attempt was made to fit the most appropriate conceptual model to each group. The models (Fig. 1) correspond to different sets of regression equations. Model A is represented by two simultaneous univariate equations: BP on age and IOP on age. Model B, a recursive model, is repre-

Table 1 *Data summary: means and standard deviations for the three groups*

	Age (years)	*Systolic BP*	*Mean BP*	*IOP (mean of 2 eyes)*	*Max IOP (max of 2 eyes)*
Normals n=90	63·6±12·3	142·0±26·4	101·9±15·8	15·4±2·7	16·0±2·9
Ocular hypertensives n=142	59·8±10·3	140·7±26·2	102·9±14·5	26·2±3·9	27·4±4·6
Stratified n=97	63·7±12·0	141·1±25·9	101·9±15·4	16·1±3·8	16·7±3·9

Table 2 *Joint distribution of low versus high IOP and systolic BP* with age in the stratified group*

	Low IOP, low BP	*Low IOP, high BP*	*High IOP, low BP*	*High IOP, high BP*	*Totals*
Age 54 and younger	4	2	8	3	17
	0·3†	−1·7	2·3	−0·8	
55–64	8	7	9	8	32
	0·7	1·1	0·5	−0·1	
65 and older	8	19	7	14	48
	−1·0	2·3	−2·3	0·8	
Totals	20	28	24	25	97

*Low IOP: less than 15·5 mmHg. Low BP: less than 140 mmHg. p=0·08. †Adjusted residual.

sented by a univariate and a bivariate regression, solved simultaneously: BP on age, and IOP on age and BP. Model C corresponds to two simultaneous univariate equations: a regression of BP on age and of IOP on BP.

Results

In the sequel, IOP denotes the mean of two eyes, and max IOP denotes the maximum of two eyes.

Table 1 summarises the raw data for each group. Table 2 shows the joint distribution in the stratified group of IOP and systolic BP (both dichotomised into 'above' versus 'below' group medians) across age levels. Table 2 also indicates that no statistical correlation with age could be found in the data with regard to the order of occurrence of raised systolic BP and of raised IOP. Indeed the adjusted residuals[19] suggest a non-significant trend to early occurrence of raised IOP and a later occurrence of BP elevation. Analogous results were obtained in the two constituent groups of patients.

Figs. 2–4 display the raw data for the stratified group by means of scatter plots of IOP against age, systolic BP against age, and IOP against systolic BP.

The results of the univariate analyses are summarised in Table 3. A highly significant positive correlation was observed between systolic BP and age in all three groups, of the order of 0·34 to 0·44. The diastolic pressure did not correlate with age nor with IOP. Numerically larger correlations were therefore observed between max IOP and systolic BP than between max IOP and mean BP.

While most correlations failed to reach significance, the max IOP—systolic BP correlation coefficients in the normal (r=−0·157) and OH (r=+0·143) groups were statistically significantly different (p=0·02). In the normal group age accounted for R^2=2·4% of the variation in max IOP. Again in the normal group systolic BP acounted for R^2=2·5% of the variation in max IOP.

In the stratified group, which had been formed to reflect the general population, the random mixing had resulted in a significant negative correlation between max IOP and systolic BP, accounting for slightly more than 4% of the variation in max IOP.

Multiple regressions of IOP and of max IOP on systolic BP and age were computed for each group. Table 4 summarises the results in terms of partial

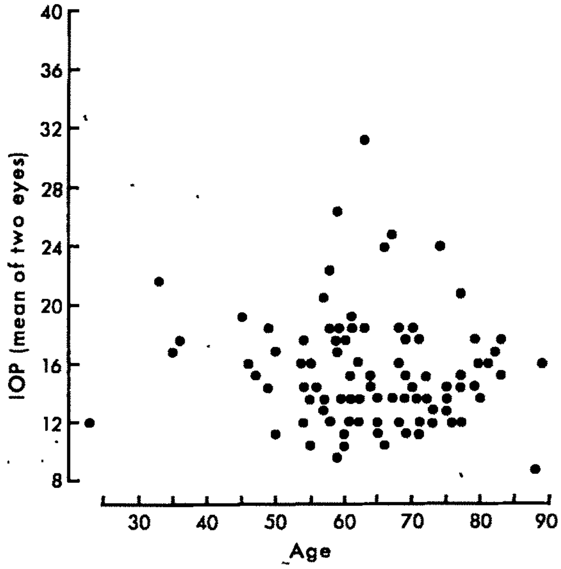

Fig. 2 *IOP on age. Data scatter plot, stratified group.*

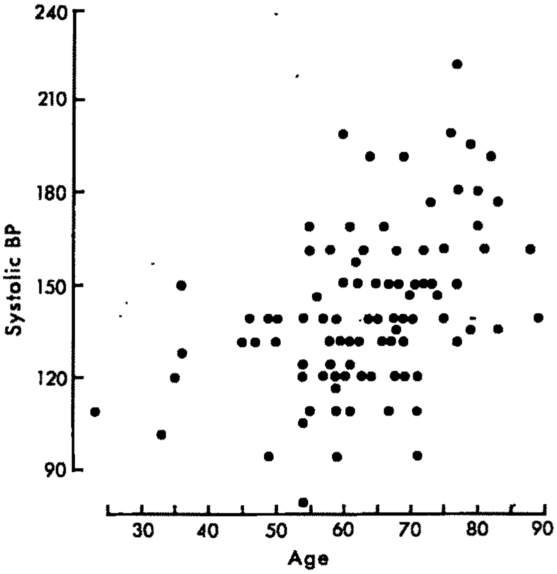

Fig. 3 *Systolic BP on age. Data scatter plot, stratified group.*

Table 3 *Paired correlation coefficients*

	Age	*IOP*	*Max IOP*
Age			
Normals		−0·169 (p=0·11)	−0·156 (p=0·12)
OH		−0·035 (p=0·67)	−0·002(p=0·98)
Stratified		−0·104 (p=0·31)	−0·091 (p=0·37)
Systolic BP			
Normals	0·446 (p=0·0000)	−0·120 (p=0·26)	−0·157 (p=0·12)
OH	0·345 (p=0·0000)	0·102 (p=0·22)	0·143 (p=0·09)
Stratified	0·441 (p=0·0000)	−0·184 (p=0·06)	−0·206 (p=0·04)

OH=ocular hypertensives.

Table 4 *Partial correlation coefficients*

Dependent variable		*IOP*	*Max IOP*
Normals	Systolic BP	−0·055 (p=0·64)	−0·110 (p=0·35)
	Age	−0·144 (p=0·22)	−0·106 (p=0·37)
OH	Systolic BP	0·164 (p=0·06)	0·163 (p=0·06)
	Age	−0·048 (p=0·59)	−0·058 (p=0·52)
Stratified	Systolic BP	−0·172 (p=0·13)	−0·206 (p=0·06)
	Age	−0·028 (p=0·80)	−0·0004 (p=0·99)

correlation coefficients. Max IOP showed a nearly significant (p=0·06) negative partial correlation with systolic BP in the stratified group and a non-significant partial correlation with age.

Analogous regression analyses were performed on younger persons only (60 years or less) in each of the groups. Results were much the same as reported above.

There was no indication that any of the three models (Fig. 1) provided an adequate description of the observations in the normal group, where the only correlation observed was between age and systolic BP. Model B could be considered to be descriptive of the ocular hypertensive group, if the level p=0·06 was taken as significant. In the stratified group, representing the general population, there was strong indication that model C, the chain model, was adequate. Path analysis suggested a direct negative correlation of the order of −0·20 to −0·24 between IOP and systolic BP, and no direct correlation between IOP and age. Any apparent correlation in this direction was likely to be almost entirely due to the strong positive correlation between age and systolic BP. Indeed, if one lets i, j, and g in Galton's model above represent, respectively, age, max IOP, and systolic BP, one obtains from Table 3, for the stratified group, that

$$r_{ij}=-0{\cdot}091,\ r_{ig}=0{\cdot}441,\ r_{jg}=-0{\cdot}206,$$

so that

$$r_{ig}\times r_{jg}=-0{\cdot}091=r_{ij},$$

with similar results for the mean IOP (mean of two eyes).

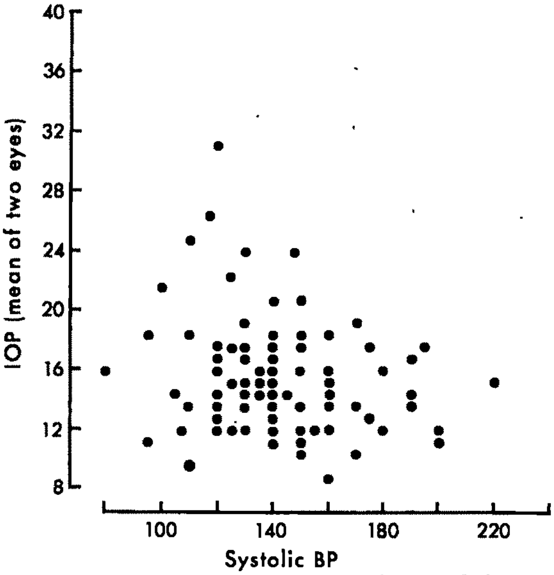

Fig. 4 *IOP on systolic BP. Data scatterplot, stratified group.*

Discussion

Out data did not show on a cross-sectional basis that a raised systolic BP occurs at an earlier age than a raised IOP. Regression analyses on younger patients failed to confirm the postulated hypothesis that, after adjusting for BP, the age effect on IOP may be more apparent in younger people.

The results reported here may help to explain the inconsistencies found in the literature correlating IOP, BP, and age. Our analyses suggested different correlations in the normal group and in the ocular hypertensive group. When a random mixture of the two groups was formed in the proportions 93% normal pressures and 7% ocular hypertensives, to reflect the composition of the general population, a distinct pattern of correlations was observed. While small sample sizes frequently led to only marginal statistical significance or non-significance, the relative sizes and signs of the coefficients formed a consistent pattern across the data. Moreover, absolute magnitudes were in close agreement with those given in the cited literature.

This work was aided by a grant from the Medical Research Council (68-1578).

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Levobunolol and metipranolol: comparative ocular hypotensive efficacy, safety, and comfort

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SUMMARY Topical levobunolol 0·5% was compared with topical metipranolol 0·6% for efficacy, safety, and comfort in 46 patients with open angle glaucoma or ocular hypertension. The study was of parallel design, randomised, double-masked, and of three months' duration. After a washout interval the study medications were instilled twice daily in both eyes. The overall mean decrease in intraocular pressure (IOP) was approximately 7 mmHg in both groups. More than 90% of patients in both groups successfully completed the study. Both agents caused slight decreases in heart rate and blood pressure. More complaints of burning and stinging were reported in the metipranolol group than in the levobunolol group. This three-month, 46-patient study showed levobunolol 0·5% and metipranolol 0·6% to be similarly effective ocular hypotensive agents.

Instilled topically into the eye, levobunolol elicits a profound, dose-related decrease in IOP in patients with ocular hypertension and glaucoma.[1,2] In a two-year, multicentre, double-masked study in 390 patients, twice daily levobunolol was found to be effective, relatively safe, and comfortable for the treatment of raised IOP.[3]

Metipranolol and levobunolol are non-cardioselective beta-adrenoceptor antagonists. Topically instilled metipranolol has been reported to be similar in efficacy to timolol in lowering intraocular pressure.[4,5] Metipranolol has been reported to elicit ocular discomfort on instillation in some patients.[6-8]

Both levobunolol and metipranolol are approved for use as topical ocular hypotensive agents in Germany as well as several other countries. The objective of this study was to compare the ocular hypotensive efficacy, safety, and comfort of levobunolol 0·5% and metipranolol 0·6%, administered twice daily, in patients with open angle glaucoma, ocular hypertension, or secondary glaucoma.

Material and methods

This study was a double-masked, parallel, randomised clinical trial of three months' duration. To be included in the study patients had to have chronic open angle glaucoma, secondary glaucoma, or ocular hypertension.

Excluded from the study were patients with known cardiac or pulmonary conditions which would contraindicate the use of beta blockers. Concomitant oral antihypertensive medication was allowed if it was essential for the patient's health and remained constant throughout the study period. Before entering the trial all patients signed consent forms that described its design, purpose, and potential risks. Patients using ocular hypotensive medication were required to undergo a washout interval of two weeks or more for beta blockers, adrenalines, or clonidine, and four days or more for muscarinic agonists. After the washout the patients were required to have an intraocular pressure (IOP) of 22 mmHg or greater in each eye. All patients received the study medication in both eyes.

After the baseline examination a drop of unlabelled study medication (0·5% levobunolol or 0·6% metipranolol) was instilled into each of the patients' eyes. The patients were instructed to continue instillation of the study medication twice daily (7 am to 8.30 am and 9.30 pm to 11 pm) for a three-month period. On follow-up examination days the morning medication was instilled after the examinations had been performed. Patients were removed from the

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trial either for adverse reaction to the study medication or for inadequate control of IOP, defined as unacceptably high intraocular pressures (22 mmHg or greater) in either eye on two consecutive morning visits 24 to 48 hours apart.

Follow-up examinations were scheduled at weeks 1, 2, 4, 8, and 12. At each examination the presence of subjective complaints, such as burning from the drops, was carefully noted.

In all statistical analyses a p value equal to or less than 0·05 was considered statistically significant. Right and left eye IOP values were averaged for analysis. Changes from baseline in IOP were calculated for each follow-up visit, and overall mean changes were calculated for the three-month study period. An analysis of variance was used for comparisons of mean IOP, heart rate, and blood pressure at baseline and mean changes from baseline among the treatment groups at each follow-up visit. An analysis of variance for repeated-measures designs[9] was used to compare overall mean IOP changes (averaged over all study visits). Within-group changes were analysed by a paired *t* test, subjective complaints with a χ^2 test, and mean age by analysis of variance.

Results

Data for 46 patients with ocular hypertension or chronic open angle glaucoma were included in the analysis. Twenty-five patients were treated with 0·6% metipranolol, and 21 patients were treated with 0·5% levobunolol. Details of demographic and glaucoma diagnosis data are shown in Table 1.

Table 1 *Demography: age, race, sex, iris colour, and diagnosis*

	Metipranolol 0·6%	*Levobunolol 0·5%*
Age		
n	25	21
Mean±SD	59·8±10·4	60·5±13·5
Minimum	40–77	20–80
Race		
White	25	21
Non-white	0	0
Sex		
Male	10	10
Female	15	11
Iris colour		
Blue	15	7
Green	3	2
Brown	6	7
Grey	1	5
Diagnosis		
Ocular hypertension	13	11
Open-angle glaucoma	12	9
Ocular hypertension and open angle glaucoma*	0	1

No significant between-group differences were noted.
*Ocular hypertension in one eye and glaucoma in the fellow eye.

Table 2 *Intraocular pressure (mmHg): changes from baseline*

Week 0 (baseline)	*Metipranolol 0·6%*			*Levobunolol 0·5%*		
	n	*Mean*	*SD*	*n*	*Mean*	*SD*
	25	*26·0*	*3·6*	*21*	*25·0*	*2·2*
1	16	−7·6	5·4	14	−6·9	2·2
2	18	−7·8	4·1	14	−7·6	4·4
4	13	−9·2	4·2	12	−6·7	2·3
8	23	−7·1	4·6	15	−7·1	3·0
12	23	−6·9	3·8	19	−6·7	2·6
Overall mean change		−7·4			−7·2	

At each visit in both groups there were significant decreases from baseline in mean IOP.

No significant between-group changes were noted at any visit or for overall mean change.

Of the 46 patients 43 successfully completed the three-month study. One metipranolol patient was removed from the trial for inadequate control of IOP and one levobunolol patient for reasons unrelated to the study. One levobunolol patient experienced shortness of breath and cramping of the chest while receiving the study medication. The patient discontinued the medication on her own and returned to her prestudy medication without sequelae.

An additional nine patients, not included in the analysis (six in the levobunolol group and three in the metipranolol group) participated in the study, though the baseline IOPs were less than 22 mmHg, in violation of the protocol entry criteria.

As shown in Table 2 and Fig. 1, the mean IOP at baseline was similar in both treatment groups. At follow-up visits the mean changes in IOP ranged from 6·7 to 7·6 mmHg in the levobunolol 0·5% treatment group and from 6·9 to 9·2 mmHg in the metipranolol 0·6% treatment group. At each visit in both groups the IOP was significantly reduced from the baseline. Analysis of overall mean changes in IOP indicated

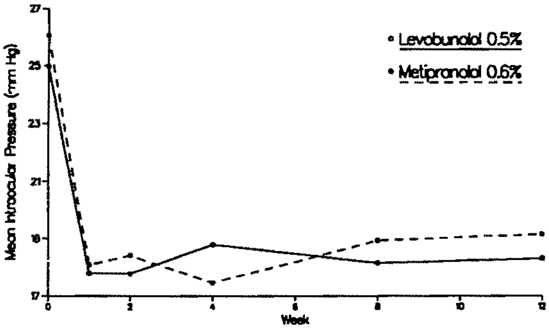

Fig. 1 *Mean intraocular pressure.*

Table 3 *Heart rate (bpm): mean changes from baseline*

Week 0 (baseline)	*Metipranolol 0·6%*			*Levobunolol 0·5%*		
	n	*Mean*	*SD*	*n*	*Mean*	*SD*
	25	*74·3*	*7·9*	*20**	*75·1*	*10·3*
1	16	−0·5	7·4	14	−0·8	8·4
2	18	0·9	10·0	14	−2·0	8·1
4	13	0·2	7·8	12	−4·5†	6·0
8	23	0·3	7·1	15	−6·9†	9·5
12	23	−1·2	9·6	18	−4·8†	7·1
Overall mean change		−0·4			−3·8	

There were significant between-group differences at Weeks 4 and 8. There were no significant differences between the groups with respect to overall mean change.
*Heart rate at baseline was not reported for one subject.
†Significant within-group changes.

decreases of 7·2 mmHg in the levobunolol treatment group and 7·4 mmHg in the metipranolol treatment group. There was no significant difference in mean change in IOP between treatment groups at any visit, or in the overall mean changes. Statistical calculations indicated that the power to detect a 2 mmHg difference between the two treatment groups was 57%.

One metripranolol patient was found to have a slight increase of blind spot in one eye, as determined by visual field examination.

Hyperaemia of the lid and/or conjunctivia was observed in four levobunolol treated patients and six metipranolol treated patients. This was mild and not sufficient to stop beta blocker therapy.

The mean heart rate is shown in Table 3. At three visits statistically significant within-group decreases were seen in the levobunolol group. At two of these visits the decreases in the levobunolol group differed significantly from those in the metipranolol group. But these changes were of limited clinical significance. In addition, the overall mean changes in both groups were less than four beats per minute and not statistically or clinically significantly different from each other. There were few changes of note in mean systolic and diastolic blood pressure in either treatment group (Fig. 2).

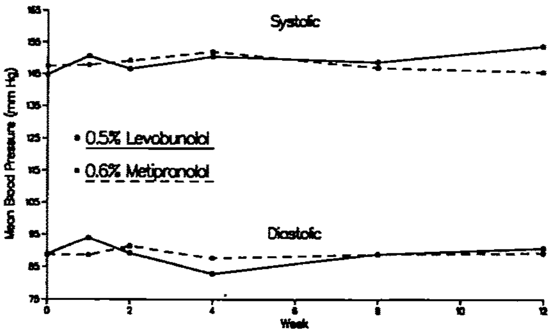

Fig. 2 *Mean systolic and diastolic blood pressure.*

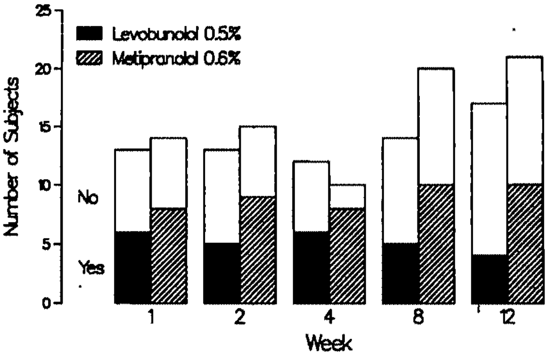

Fig. 3 *Frequency of stinging or burning.*

The incidence of stinging or burning is shown in Fig. 3. At each visit eight to 10 (48%–80%) metipranolol treated patients reported stinging or burning, in contrast to four to six (38%–56%) of the levobunolol treated patients. This difference was not statistically significant. No other patients' complaints were noted.

Discussion

The objective of this study was to evacuate the efficacy and safety of two β_1 and β_2-adrenoceptor antagonists, levobunolol and metipranolol, for the treatment of raised intraocular pressure. We found both levobunolol and metipranolol to be effective in lowering intraocular pressure an overall average of 7 to 7·5 mmHg, which is similar to previous reports for both drugs.[3,7,8] However, one must be aware that the power of this study to detect a 2 mmHg difference was only 57%. Thus there was a 43% chance that there could have been a 2 mmHg difference which was not detected by this study due to sampling variability.

As in previous reports[7,8] metipranolol was found to cause burning and stinging. In the present study reports of burning and stinging were more frequent in metipranolol treated than in levobunolol treated patients. This difference was not statistically significant. However, the data from the both the present study and a previous comparison of metipranolol and levobunolol[4] suggest that metipranolol may be less comfortable than levobunolol in glaucoma patients.

Decreases in heart rate and blood pressure, as observed in this study, have previously been reported for both levobunolol and metipranolol[3,7,8] and are expected from topical therapy with a beta blocker.

The one apparently drug-related adverse experience in the study was a pulmonary reaction in the levobunolol treatment group. While this 72-year-old patient had no history of pulmonary disease, it is possible that he had occult pulmonary disease which was exacerbated by the beta blocker treatment. Clearly all topical beta blockers may induce a pulmonary reaction in sensitive patients.[10-12]

In the present three-month study levobunolol and metipranolol were found to be similar in efficacy. However, as glaucoma is a long-term disease, additional studies will be required to determine the comparative efficacy of these agents in long-term use.

The authors acknowledge the technical assistance of Cathy Bruns, BA.

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Prostaglandin metabolism and intraocular pressure

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SUMMARY The plasma lipid alterations characteristic of essential fatty acid deficiency (EFAD) generally appear one to two weeks after the initiation of fat free parenteral nutritional (PN), and may be associated with a reduction in prostaglandin (PG) formation. In the present study the relationship between exclusion of fat from the diet and changes in intraocular pressure (IOP) and PGE_2 plasma levels were studied in 28 patients. The results indicated that three weeks after the omission of dietary fat a significant reduction in IOP levels occurred which persisted throughout the follow-up period of 7 (SD 1·2) weeks. Plasma PGE_2 levels were also significantly reduced in patients on fat free PN for three weeks as compared with levels measured while patients were on a fat containing diet. This clinical observation is not yet understood and might be related to changes exerted by fatty acid deficiency.

Patients on fat-free parenteral nutrition (PN) may show the alterations in plasma lipid pattern characteristic of essential fatty acid deficiency (EFAD) as early as a week or two following initiation of the diet.[1-3] These changes involve a decrease in plasma levels of linoleic and arachidonic acids, and a significant increase in 5.8.11 eicosatrienoic acid.[1] The clinical manifestations of EFAD, desquamative dermatitis, hair loss, thrombocytopenia, and poor wound healing,[2] appear later in the course of this disorder.[1,3]

Decreased prostaglandin (PG) production in EFAD may occur as a result of the reduction in arachidonic acid and the increase in 5.8.11 eicosatrienoic acid serum levels, since the latter is a potent inhibitor of PG synthesis and the former is the main substrate of PG production.[4,5] PGs are mainly known for their mediatory role in inflammation in most organs,[6] including the eye.[7,8] Likewise it is well established that exogenous and endogenous PGs can give rise to acute elevation of intraocular pressure (IOP).[9-12] However, when applied in low doses PGs cause a prolonged reduction in IOP.[13-16]

The present study was undertaken to investigate the relationship of fat free nutrition, PGE_2 plasma levels, and IOP.

Subjects and methods

The subjects were 18 female and 10 male patients aged 21 to 60 years who were on fat free PN. The age distribution and the diagnosis which necessitated the fat free PN are given in Table 1.

Fat free PN was the sole source of alimentation of all 28 patients for an average period of 7±1·2 weeks (mean±SD). The diet consisted of a mixture of crystalline amino acids, hypertonic glucose, electrolytes and vitamins. Later, fat supplementation (intralipid 10%, containing a mixture of essential fatty acids) was added for further 9±2·1 weeks.

Though patients involved in this study were suffering from major illness, owing to the daily high calorie input made possible by the PN some were gaining weight, while none lost weight. Likewise there was

Table 1 *Distribution of patients on PN according to age, sex, and diagnosis*

Age (yr)	*Sex*		*No. of patients*
	Female	*Male*	
21–44	5	3	8
45–59	7	6	13
60 and over	5	2	7
Total			28
Diagnosis			
Ulcerative colitis			5
Crohn's disease			7
Neoplastic diseases			11
Diverticulitis			1
Lymphoma			4
Total			28

Correspondence to Dr N Naveh-Floman.

no fall in systemic blood pressure in these patients while they were on fat free diet. Supplementation of fat in these patients did not affect their general health, blood pressure, or body weight.

During the study the ophthalmologist involved was unaware of the diagnosis of the patient or his diet.

The IOP was measured at the bedside under topical anaesthesia with benoxinate hydrochloride 0·4% and a Schiøtz tonometer, with both 5·5 and 10·0 mg weights. The average of six measurements, three with each weight, was taken, and the deviation for each set of three measurements did not exceed 10–15%. All measurements were performed on all patients by the same ophthalmologist at the same time of day (between 10 and 12 am). Scleral rigidity was calculated for each patient by means of the paired Schiøtz tonometer reading as described.[17] Patients with gross signs of inflammation or other ocular pathology were excluded. Measurements were made weekly—before the patients were started on the fat free PN, during the fat free PN, and after the patients received fat supplementation.

PGE$_2$ plasma levels were determined in 14 patients by radioimmunoassay of a PGE$_2$ metabolite (13,14-dehydro 15-keto PGE$_2$) using a specific antiserum.[18]

Blood samples for PGE$_2$ analysis were drawn into glass tubes containing EDTA (3·7×10^{-3}M final concentration) and indomethacin (10^{-6}M final concentration). They were then centrifuged at 2000 *g* for 15 minutes at 40°C. The plasma fraction was isolated, frozen, and stored at −70°C. Blood samples were drawn three weeks after fat free PN was initiated and then after three weeks of fat supplementation of the diet.

Data were statistically evaluated by Student's *t* test.

Results

The effect of dietary fat on IOP is shown in Table 2. Ocular pressure was significantly reduced on the third week of fat free PN in comparison with levels measured in these same patients while on normal diet (p=0·0001). Supplementation of fat to the diet for three weeks was followed by an increase in ocular pressure to levels observed when these patients were on a normal diet (p=0·001). Comparison of IOP measurements taken when patients had been on fat free diet for three, five, and seven weeks showed they were not significantly different (p=0·85). The mean IOP of patients on fat free PN was lower by 3·53±2·20 mmHg than the mean level measured while they were on fat supplemented diet (p=0·0001). Comparison of mean scleral rigidity for patients while on fat free PN and following fat supplementation was not significantly different (0·0196±0·0030 and 0·0189±0·0038 respectively).

Table 2 *Effect of dietary fat on intraocular pressure*

No. of weeks following dietary changes	*Intraocular pressure (mmHg), mean±SD*		
	Normal diet	*Fat free PN*	*Fat supplemented PN*
	14·38±2·80 (28)*		
3		10·65±2·60 (28)	13·92±3·04 (28)
5		9·50±3·20 (23)	14·18±2·09 (23)
7		9·90±5·09 (17)	14·38±2·80 (15)

*Numbers in brackets indicate the number of patients included.

The effect of dietary fat on PGE$_2$ plasma levels was studied in 14 of the patients and is detailed in Table 3. The results indicated that PGE$_2$ plasma levels were significantly lower in the patients on a completely fat free PN for three weeks than in patients on a fat supplemented PN for the same length of time (p=0·0004). The mean reduction in PGE$_2$ levels was 0·148±0·0004 pg/ml (p=0·0079).

Discussion

EFAD occurs as a complication of fat free PN in both infants and adults and is already evident one to two weeks after initiation of this diet.[1-3] In patients on a normal diet linoleic acid—the only essential fatty acid in man—is elongated and desaturated to form arachidonic acid. Omission of fat causes linoleic acid deficiency with an accumulation of oleic acid, which is converted to 5.8.11 eicosatrienoic acid rather than arachidonic acid. This in the course of EFAD two processes occur that reduce PG formation: the increase in 5.8.11 eicosatrienoic acid, a potent inhibitor of PG production,[5] and the decrease in availability of arachidonic acid, a main substrate of PG synthesis.[1]

It is generally accepted that exogenous or endogenous PGs applied to the eye cause an acute rise in IOP associated with development of flare and other signs of inflammation.[9-12] However, low doses of

Table 3 *Effect of dietary fat on prostaglandin E_2 (PGE$_2$) plasma levels*

	PGE$_2$ plasma levels (pg/ml), (mean±SD)*
Fat free diet (n=14)†	0·015±0·004
Fat containing diet (n=12)	0·029±0·01

*Determined after patients had been on either dietary regime for three weeks. †n=the number of patients studied.

PGE_2 and $PGF_{2\alpha}$ topically applied to the rabbit, owl monkey, cats, or rhesus monkey eye cause a highly significant decrease in IOP distinctly different in each of the species studied.[13-15] This ocular hypotension in cats and rhesus monkeys was maintained during the course of a long term topical treatment with PGE_2 and $PGF_{2\alpha}$ with negligible signs of irritation.[16] In addition PGs are believed to act as mediators of adrenergic neurotransmission by a negative feedback mechanism in the eye and various other organs.[19,20]

PGs have been also suggested to have a modulatory role in the ocular pharmacological effect of sympathomimetic amines in vivo based on indomethacin capability to inhibit in rabbits[21,22] and humans[23] the hypotensive effect of topically applied epinephrine. Recently evidence for alpha-adrenergic stimulation of PGs released from rabbits and bovine irides was reported.[24,25] PGE_2 was the major PG released.[24] However, it is as yet unknown how PGs exert their effect on IOP, especially in man.

In the present study the omission of fat from the diet was associated with a significant decrease in ocular pressure compared with levels noted while patients were on a normal diet. Decrease in ocular pressure was not associated with changes in scleral rigidity, though rigidity in the two groups of patients involved in our study was somewhat lower than normal (normal value for K is 0·0215).[17] The reduction in IOP persisted as long as the patients were on fat deficient regimen, during a mean follow-up period of 7±1·2 weeks, and the pressure returned to normal on fat supplementation.

The development of EFAD was associated also with a significant decrease in PGE_2 plasma levels when compared with normal levels. These results are in agreement with those of Freund *et al.*,[26] who showed that PGE_2 metabolite levels were reduced on exclusion of dietary fat. However, lowering levels of PGE_2 metabolites in plasma does not necessarily mean a decrease in synthesis of these products. The association of IOP reduction, EFAD, and reduced plasma levels of PGE_2, though clinically interesting is not fully understood and might not necessarily indicate a casual relationship. The patients studied suffered major sickness, and therefore other factors besides EFAD might have affected changes in ocular pressure and PGE_2 levels.

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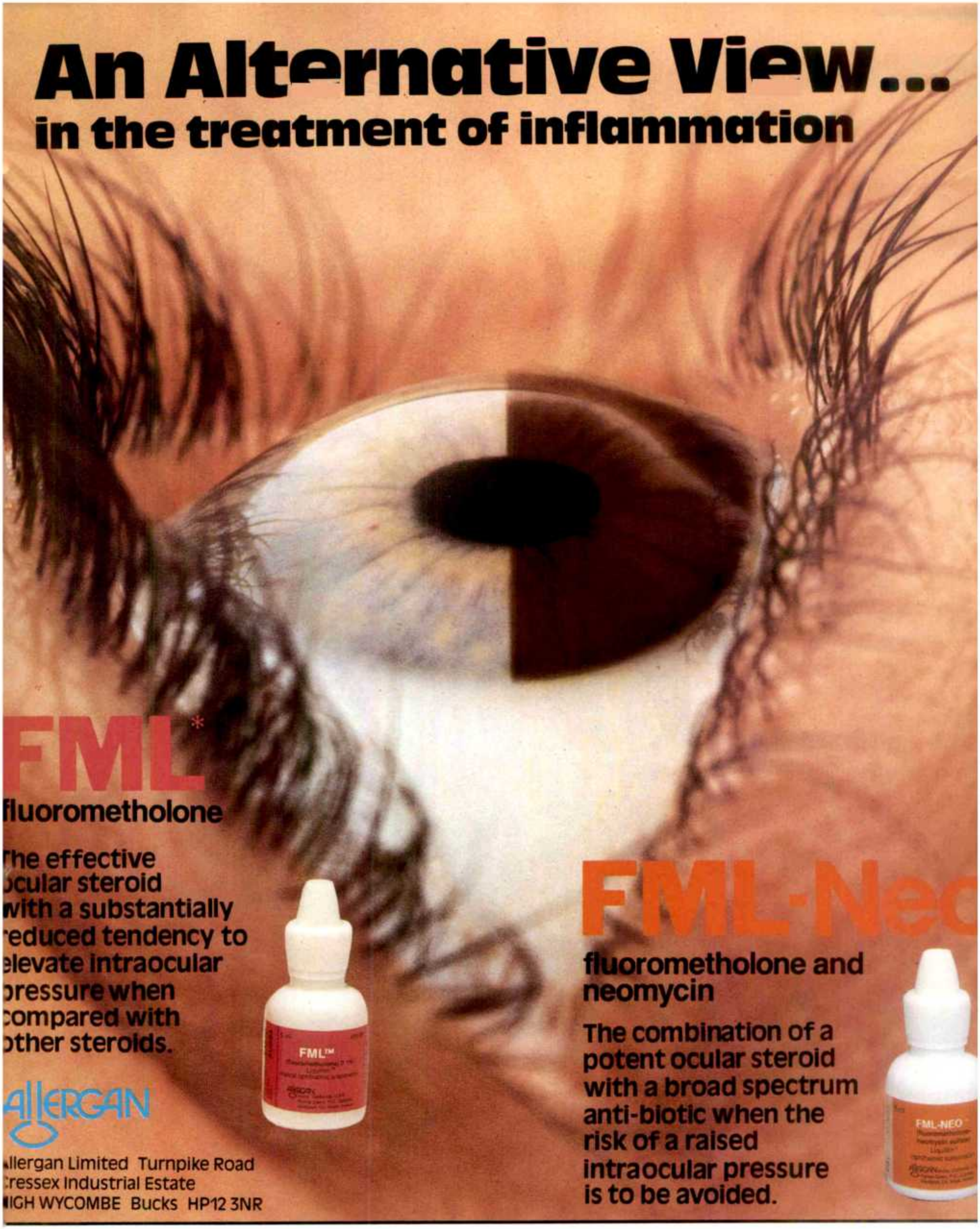

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Ocular tuberculosis, fungal diseases of the eye and hypersensitivity to any of the components of the drug. **Warnings** As for F
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increase in the prevalence of persons sensitive to neomycin. The possibility of such a reaction should be borne in mind. If sen
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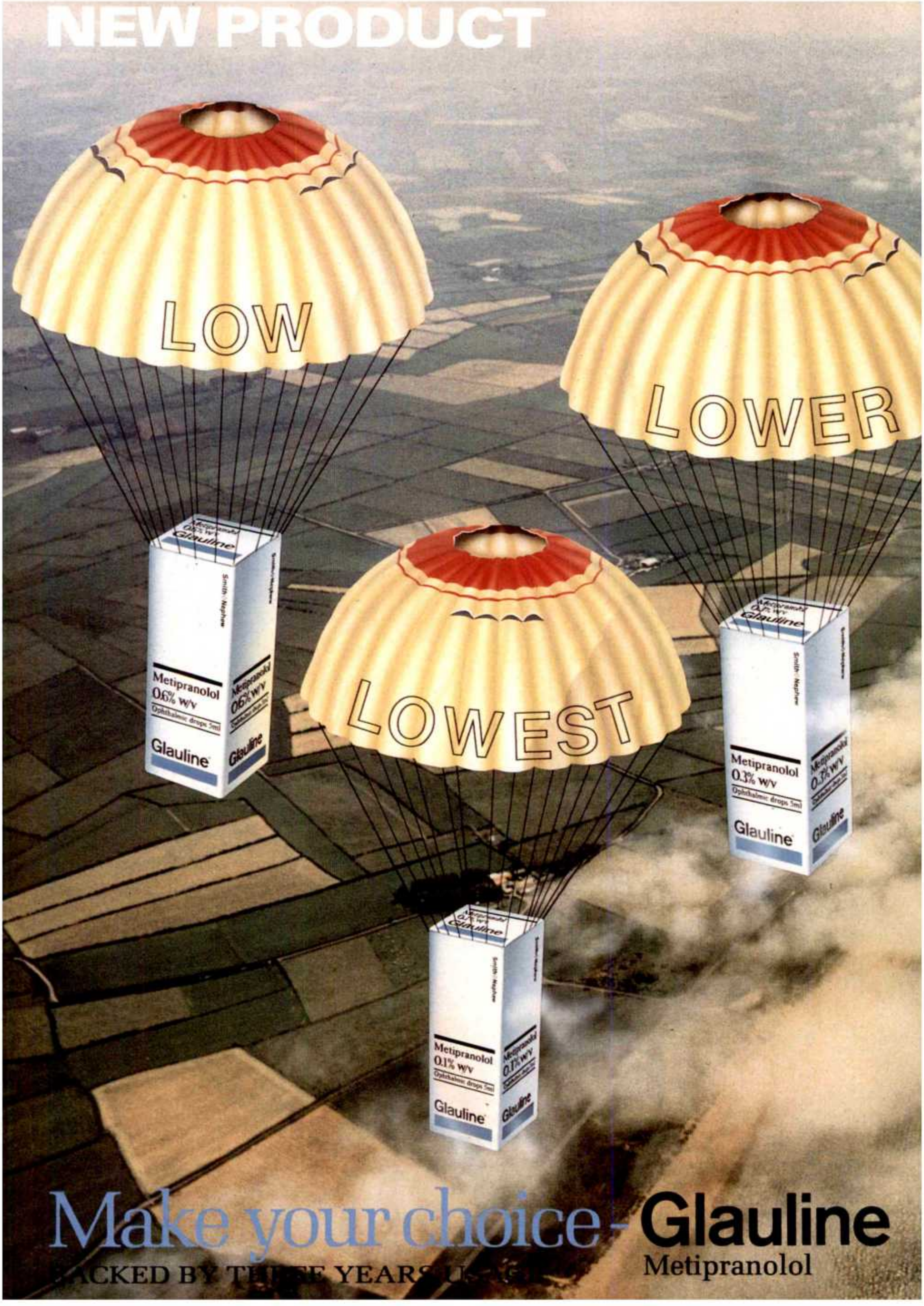
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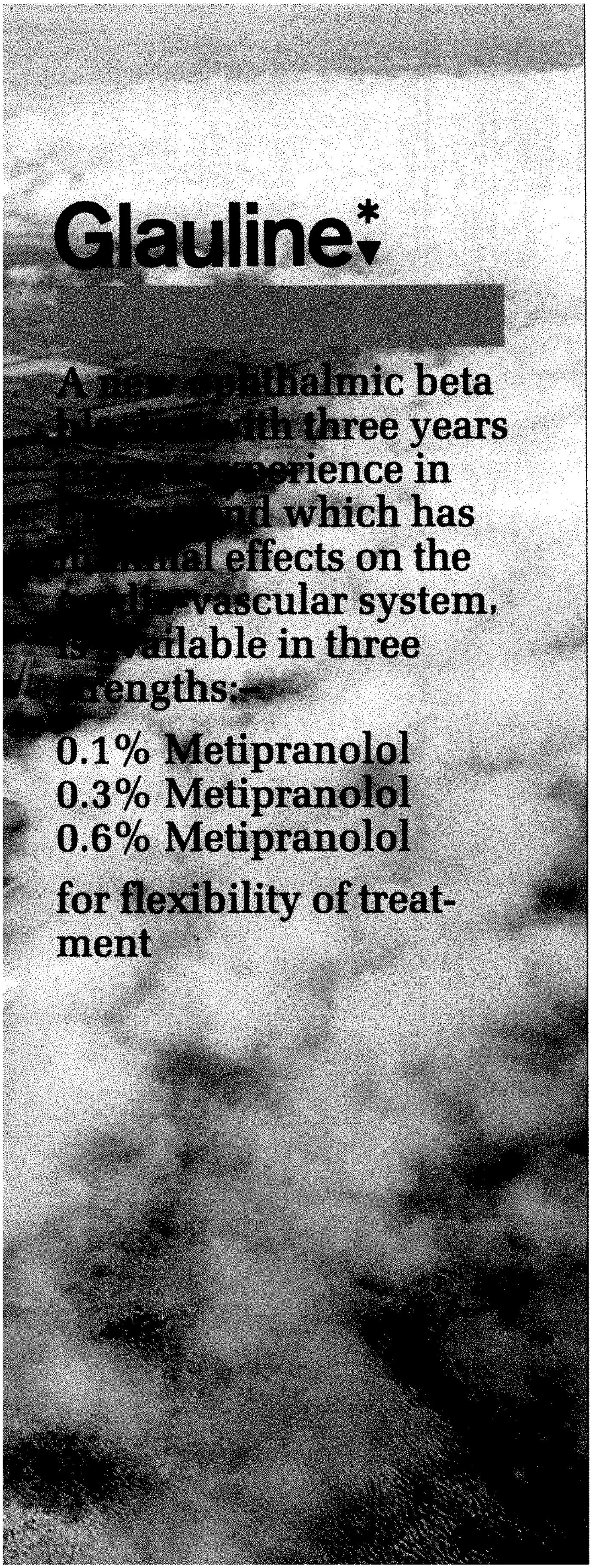

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Glauline is a beta adrenoceptor blocking agent used in the topical treatment of chronic open-angle glaucoma and other conditions in which intra-ocular pressure is elevated above normal levels.

DOSAGE AND ADMINISTRATION

The recommended dosage is one drop instilled into the affected eye twice daily. Newly diagnosed patients should be treated in the first instance with Glauline 0.1%, changing to a higher strength if adequate control is not achieved or maintained. Patients on existing therapy, whether or not this is to be continued, should receive 0.3% Glauline and the intraocular pressure of all patients should be monitored regularly (e.g. every 4-6 weeks).

Use of the 0.6% strength is only recommended in patients who are not controlled on the lower strengths of Glauline.

CONTRA-INDICATIONS, WARNINGS ETC.

The use of Glauline is not recommended in patients with obstructive airway disease, cardiac failure or hypersensitivity to metipranolol. Beta blockers should not be given with verapamil and neither drug should be administered within several days of discontinuing the other. As absorption into the circulation is possible, Glauline should be used with caution in patients already receiving similar drugs by mouth. In particular, care should be taken in patients with sinus bradycardia and greater than first degree heart block.

Although there is no evidence to suggest that metipranolol has teratogenic properties, its use during pregnancy should be avoided, unless the potential benefits are considered to outweigh the possible hazards No clinical trials in children have been carried out.

Glauline should not be used in patients fitted with soft (hydrophilic) contact lenses.

PHARMACEUTICAL PRECAUTIONS

Glauline should not be diluted or dispensed from any container other than the original bottle. It is potent for three years unopened, but as with other eye drops the contents of each bottle should be discarded one month after opening.

LEGAL CATEGORY

POM

PACKAGE QUANTITIES

Glauline is supplied as a sterile ophthalmic solution in a 5ml plastic dropper bottle.

FURTHER INFORMATION

Glauline has little or no effect on pupil size or accommodation.

Glauline is generally well tolerated but some patients may complain of a slight stinging which soon passes off. Transient headaches have also been reported.

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Neodymium-YAG laser iridotomy in angle closure glaucoma: preliminary study

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SUMMARY A prospective short-term preliminary clinical study to evaluate the efficacy and immediate complications of Q-switched Nd-YAG laser iridotomy in the treatment of acute and chronic angle closure glaucoma is described. The follow-up period ranged from four to 10 months. Of 40 eyes treated 36 (90%) required a single lasing session for patency (19, one application; 17, two applications), and four eyes (10%) required two sessions. Closure of the iridotomy site following Nd-YAG lasing due to pigment epithelium proliferation occurred in 10% of eyes, an incidence remarkably lower than that of argon laser iridotomy. Transitory closure or diminution of a prior patent iridotomy during the first hour after lasing was observed in 6·7% of eyes. Patency was again noted up to three weeks later and remained unchanged. Immediate postoperative complications included a marked increase in ocular pressure (42% of eyes), minimal transitory bleeding, and transitory localised corneal oedema at the lasing site. Persistent iridocorneal adhesion at the lasing site was noted in three eyes, and localised lenticular opacities, of non-progressive type, were observed in one eye.

Argon laser iridotomy is at present[1-7] the procedure of choice in the United States for the treatment of pupillary block glaucoma. However, despite modified argon laser techniques, difficulties in penetration of light blue and dark brown irides have been widely reported.[8-12]

The Q-switched neodymium (Nd)-YAG laser causes tissue disruption by optical breakdown and resulting shockwave, making iris colour irrelevant.[13] Initial reports on the efficacy of the Nd-YAG laser indicate important advantages in this method.[13-16] In the present study the ability of the Nd-YAG laser to produce iridotomy, and the complications associated with this procedure, are further investigated.

Materials and methods

Q-switched Nd-YAG laser iridotomy was performed in 32 patients (40 eyes), divided into three groups: 18 patients (24 eyes) with chronic angle closure glaucoma; six patients (eight eyes) with acute angle closure glaucoma; and eight patients (eight fellow eyes) in whom acute angle closure glaucoma had occurred in the other eye some time in the past. Chronic angle closure glaucoma was diagnosed in those patients without a clear history of an acute attack who had narrow angle approaches and peripheral anterior synechiae (PAS) in at least one eye. Patients with secondary angle closure glaucoma were excluded from the study. The distribution of patients according to age, sex, and diagnosis is given in Table 1.

The patients were admitted to the series sequentially over a period of three months and were aware of the investigative nature of the therapy. The follow-up period ranged from four to 10 months. Six patients (eight eyes) in whom previous argon laser procedures had failed were included.

Prior to laser therapy all patients underwent ophthalmic examination, including Snellen visual acuity testing and Goldmann applanation tonometry. Pilocarpine hydrochloride 2% was administered 30 minutes before surgery.

The laser procedure was performed on an outpatient basis with topical anaesthesia (proparacaine 0·5%). The Fankhauser Q-switched Nd-YAG laser (LASAG, Thun, Switzerland) was used in all cases,

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Table 1 *Distribution of patients according to age, sex, and diagnosis*

Diagnosis	*No. of patients*	*Age (years)*			*Sex*	
		55–65	*66–75*	*75*	*F*	*M*
Chronic angle closure glaucoma	18 (24)*	5	10	3	10	8
Acute angle closure glaucoma	6 (8)	2	3	1	4	2
Fellow eyes to eyes with prior acute angle closure glaucoma	8 (8)	3	5		4	4
Total	32 (40)	10	18	4	18	14

*Figure in brackets indicates number of eyes involved.

and a Russel-Fankhauser iris lens was placed on the eye. The Fankhauser method for power settings consisted of a burst of 2 to 4 pulses, with selected energy levels varying from 6 to 10 mJ in the multimode train. Iridotomy was located, preferably basally, at an iris crypt in the superior nasal or temporal quadrant.

Successful penetration was manifested intraoperatively either by a gush of aqueous humour containing pigment epithelium particles from the posterior chamber, or by visibility of the anterior lens capsule. If the first burst failed to create a patent iridotomy, a second burst was fired during the same session, aimed at a different site.

The treated eyes were observed for iridotomy patency, changes in ocular pressure, and bleeding for the first five postoperative minutes. The presence of inflammation and debris in the anterior chamber, lens changes, gonioscopic appearance, and synechial formation were noted at hourly intervals for the next four hours. Patients returned for follow-up at one day, one week, and two weeks after treatment and at monthly intervals thereafter.

Topical steroids, four times daily, were started on the day of laser treatment and continued until the end of the first postoperative week. Preoperative glaucoma medications were continued as necessary. In cases in which ocular pressure increased to more than 10 mmHg over baseline during the first four postoperative hours, oral glycerine 3 ml/kg body weight was given. Patients in this group were followed up at 90-minute intervals until ocular pressure returned to normal.

Results

Penetration was achieved during one session with either one or two laser applications in 36 eyes (90%); a second session was required for four eyes (10%) (Table 2). Of the 36 eyes in which a patent iridotomy was achieved during one laser session 19 needed only a single laser application, and 17 required a second application.

The total energy necessary to produce iridotomy ranged from 20·8 to 97·0 mJ (mean, 62·3±12·4 mJ), with bursts at mean levels of 9·6±2·1 mJ with 2 to 4 pulses. The mean total energy levels used for the second application were considerably higher than those used with the first (42·1±11·8 and 26·2±3·4 mJ, respectively; p=0·001) (Table 2).

In four eyes the iridotomy closed within six weeks after treatment. In two dark brown eyes and one light blue eye closure was due to proliferation of pigment epithelium. In the fourth eye the initial opening was slit-like and closed two weeks after treatment without clear evidence of pigment epithelium proliferation. In all four cases a repeat laser session proved effective in reopening the iridotomy site.

During laser application most patients complained of a severe discomfort, causing many to jerk their head back suddenly. In most cases the pain subsided shortly after treatment. The iridotomy site was typically elongated, with ragged edges, and was sometimes surrounded by iridoschisis-like areas.

All patients showed an immediate severe response in the anterior chamber, consisting mostly of pigmented debris of +2 to +3.

In six eyes an unusual sequence of events was noted. During laser treatment an opening was clearly obtained, but soon thereafter the opening narrowed dramatically, so that endotomy patency was questionable or negative. In two of these cases the

Table 2 *Energy requirements for Nd-YAG laser iridotomy*

No. of laser sessions	*No. of applications*	*Total energy (mJ): mean (SD)*	*No. of eyes*		*Diagnosis*		
			Blue	*Brown*	*CACG*	*AACG*	*Fellow eye*
One session	1 application	30·5 (6·1)	10	9	12	4	5
One session	1st application 2nd application	26·2 (34·0) 42·1 (11·3)	11	6	9	3	3
Two sessions	1st session 2nd session	48·0 (14·0) 85·0 (12·0)	2	2	2	1	1

CACG=chronic angle closure glaucoma. AACG=acute angle closure glaucoma.

Table 3 *Postoperative complications of Nd-YAG laser iridotomy*

Complications		*No. of eyes*	*Iris colour*	
			Brown	*Blue*
Ocular pressure increase*	10 mmHg	17	5	12
	10 mmHg	9	6	3
Bleeding	'Streaky'	7	5	2
	hyphaema 5%	1	1	—
Localised corneal oedema	Transitory	3	—	3
	Persistent	1	1	—
Iridocorneal adhesion		3	1	2
Focal lenticular opacities		1	1	—

*Difference between IOP one hour after iridotomy and preoperative (baseline) value.

progressive rapid closing of the iridotomy was actually observed while the treatment lens was still on the eye. In the remaining four cases diminution of the iridotomy was noticed at the 60-minute follow-up period. However, in each of these eyes widening of the iridotomy eventually occurred, as the iridotomy was patent at the two-week follow-up examination and remained unchanged during the entire follow-up period of more than three months.

The immediate postoperative complications are shown in Table 3. Seventeen eyes (42%) showed an increase in ocular pressure of more than 10 mmHg over baseline (the mean ocular increase was 23·0 (SD 5) mmHg); these included 12 eyes (28%) with increases of more than 18 mmHg over baseline. This increase in ocular pressure did not correlate with the preoperative ocular pressure, the degree of ocular inflammation, the energy requirements for iridotomy, or the amount of iris bleeding. However, 12 of the 17 eyes (71%) with an immediate increase in pressure postoperatively had blue irides, whereas the percentage of blue irides of all eyes involved in the study was 58% (Table 2).

Minimal bleeding from iris vessels which lasted up to three minutes occurred in eight eyes (20%). Only one eye showed formation of a 5% hyphaema, which cleared the following day (Table 3).

In three eyes localised corneal oedema with Descemet folds corresponding to the area of laser application was noted a few hours after lasing and lasted up to four days. This transitory corneal damage occurred in eyes in which Nd-YAG iridotomy was performed soon after resolution of an attack of angle closure glaucoma, while the eyes were still inflamed and with the anterior chamber unusually narrow.

Iridoschisis-like changes surrounding the iridotomy opening were observed in many of the patients; however, persistent adhesion of the schitic iris stroma to the cornea was noted in only three patients at the two-week follow-up visit. Persistent localised corneal opacity with Descemet break overlying the laser treated site was observed in one patient (Table 3).

Focal lenticular opacity without rupture or break of the anterior lens capsule occurred in one case, and some pigment deposition on the lens overlying the iridotomy site was observed in another (Table 3).

Discussion

Q-switched Nd-YAG laser iridotomy in humans has so far been studied for a short time in a limited number of eyes, achieving penetration in all cases with only minor and transient complications.[13-15] In our series patent iridotomies were created after a single lasing session in 36 of the 40 glaucomatous eyes studied (90%) and after two sessions in the remaining four eyes (10%). In previous studies on Nd-YAG laser iridotomy a patent iridotomy was created in one treatment session in every case.[13-15] Robin and Pollack[15] used both the American Medical Optics YAG-1000 and the Coherent-JK prototype Nd-YAG lasers, whereas Fankhauser[14] and Klapper[13] used a Nd-YAG laser similar to the one used herein.

The total energy levels used in our work in eyes successfully penetrated within one session were compatible with those used by Fankhauser[14] and Klapper.[13] However, in the present study bursts of 6 to 10 mJ of 2 to 4 pulses each were applied in the multimode train; Fankhauser[14] and Klapper[13] applied bursts of 4 to 8 mJ of 4 pulses each in the fundamental mode. The failure to penetrate the iris within one session in 10% of eyes in the present study might be partly due to these differences in technique, though other factors may also have been involved (this being our initial experience with the Nd-YAG laser). Interestingly, of the four eyes that required two Nd-YAG lasing sessions to achieve penetration two dark brown eyes of one patient had undergone argon laser iridotomy twice prior to Nd-YAG laser iridotomy with negative results.

Closure of the iridotomy site following Nd-YAG lasing due to pigment epithelium proliferation occurred in four of the eyes (10%) included in this study—three darkly pigmented irides and one light blue iris. Two of the darkly pigmented eyes belonged to the same patient with a history of repeated closure of argon laser iridotomy prior to iridotomy by Nd-YAG laser.

Ours are the first reported cases of pigment epithelium proliferation resulting in iridotomy closure following Nd-YAG lasing in patients with angle closure glaucoma. (The only cases of Nd-YAG endotomy closure thus far have been reported by Klapper[13] in patients with neovascular glaucoma and uveitis.) The incidence of closure of Nd-YAG laser iridotomy as shown in our series is still remarkably lower than that of argon laser iridotomy, which requires reopening in one-third of cases.[3 4 6] This difference has been attributed to the differing effects of argon thermal energy and Nd-YAG shockwave on pigment epithelium cell disruption.[16] However, full evaluation of the incidence of Nd-YAG iridotomy closure requires larger and longer-term studies.

Immediate postoperative closure or diminution of a prior open endotomy to the degree that patency became questionable was observed in 6·7% of eyes. However, in each of the eyes involved the closure or diminution was transitory, as patency was observed up to three weeks following lasing, and iridotomy size remained unchanged thereafter throughout the entire follow-up period of more than three months. The mechanism of the immediate transitory closure or diminution of the endotomy following Nd-YAG lasing has not yet been described and may involve stromal disruption by shockwave. Continuous progressive widening of Nd-YAG iridotomy at later stages has been observed in animals but has not yet been seen in humans,[16] while widening of argon laser iridotomy during the follow-up period in humans is widely accepted and was recently documented.[17]

The immediate postoperative complications were characterised by a marked increase in ocular pressure within the first two postoperative hours, noted in 42% of eyes included in our series. In 28% of eyes the pressure remained elevated by more than 10 mmHg over baseline despite hyperosmotic treatment during the first 4 to 6 hours. There was no correlation between the increase in ocular pressure and the energy levels used, the degree of anterior chamber inflammation, or the presence of iris bleeding. Robin and Pollack[15] found that in 65% of eyes treated with Nd-YAG laser iridotomy there was some increase in ocular pressure (range 1 to 38 mmHg) during the first three postoperative hours, with only two patients requiring treatment with glycerine. In the series of Fankhauser[14] and Klapper[13] a rise in ocular pressure occurred in only 2 of 20 eyes treated. This low incidence of ocular pressure increase after lasing, as compared with ours, might be due to the differences in technique but requires further evaluation, as total energy levels did not differ in these studies.

In our series iris bleeding, evident in 20% of eyes, was minimal and was absorbed rapidly after onset. This finding is in good agreement with previous data showing frequent bleeding following Nd-YAG laser iridotomy in humans.[15]

In our series corneal lesions following Nd-YAG laser iridotomy occurred in five eyes (12·5%). These included three eyes with transitory corneal oedema above the application site and one eye with non-progressive corneal opacity at the lasing site. Three of the eyes with corneal lesions were characterised by narrow chambers a few days after resolution of an acute attack of pupillary block. The number of corneal lesions following pulsed lasing is inversely proportional to the distance of optical breakdown.[18 19]

Iridoschisis-like changes surrounding the laser site, as well as ragged endotomy edges (unlike the sharp edges found following argon iridotomy), were observed in many patients and were uneventful. However, in three eyes with exceedingly narrow chambers and an iridotomy located peripherally persistent iridocorneal adhesion at the endotomy site was noted at the two-week follow-up visit. These are the first reported cases of iridoschisis-like changes at the laser site, and it is our impression that they are not due to inaccurate focusing and are hardly surprising from the explosive nature of iris photodisruption.

Lenticular opacities observed in our series were of a non-progressive nature. Lenticular damage following Nd-YAG iridotomy might be attributed to the extension of the laser explosion to a distance of 450 μm from the lasing site, as shown recently.[19]

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Silicone oil with high specific gravity for intraocular use

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SUMMARY Silicone oil with a higher specific gravity than that of intraocular fluid or polydimethylsiloxane may have special indications in vitreoretinal surgery. Trifluorsiloxane is such a substance, and therefore its biological compatibility was investigated in rabbit eyes. It was found that this substance was clinically well tolerated within the observation time of up to 6 months, even if there was some neovascularisation from the inferior limbus. Histologically both an inflammatory response and tissue impregnation were more pronounced than with normal polydimethylsiloxane.

After the first introduction of silicone oil in the treatment of severe tractional retinal detachment by Cibis[1] this substance was thought to be a last resort for desperate cases with a doubtful outcome. However, since Scott[2] and later Zivojnovic *et al.*[3] combined the injection of silicone oil with extensive vitrectomy this substance has gained widespread successful use as an intraocular tamponade in the microsurgical management of retinal detachment due to advanced proliferative vitreoretinopathy. While most of the oils now in use differ considerably in viscosity and chemical purity (Gabel *et al.*, in press), all have a specific gravity less than that of the intraocular fluid. However, a tamponade of lower specific gravity may not be optimal for all cases, particularly for patients having inferior tears. We have therefore investigated the biological reaction to a silicone oil with a higher specific gravity than intraocular fluid. Such a substance was first mentioned by Watzke[4] in 1967, but the suggestion was not followed up at the time. Now a silicone oil with high specific gravity has become available. It is produced in a special way to achieve a high level of chemical purity in terms of absence of low molecular components and catalyst residue. However, from a chemical point of view (Burkhardt, personal communication) it is more difficult to purify trifluorsiloxane than polydimethylsiloxane. It therefore seemed to us that careful studies of biological compatibility in animals were essential before its use in patients.

Material and methods

The only high specific gravity silicone oils available at present are fluorised silicone oils. For this study polytrifluoropropylmethylsiloxane (FS) was used. It first underwent a special treatment to eliminate low molecular components and catalysts as postulated for polydimethylsiloxane (PDMS) by our group.[5] The absence of catalyst was proved by *x*-ray fluorescence analysis. Details of its chemical and physical properties are listed in Fig. 1.

A total of 21 eyes of chinchilla grey rabbits were prepared for silicone oil injection and extracapsular lensectomy under ketamine-xylacin anaesthesia. The lensectomy was performed to increase the total volume available for an injection of silicone oil as well as to obtain access for silicone oil to the anterior segment. The posterior capsule was left in place in three eyes, to confine silicone oil to the posterior segment. Four to eight weeks after lensectomy pars plana vitrectomy with or without removal of the posterior lens capsule was performed on 17 eyes. A fluid gas exchange preceded the injection of silicone oil in 15 eyes. We employed two types of controls: two vitrectomised eyes received the normally used silicone oil of low specific gravity after removal of the posterior lens capsule, and four eyes were subjected only to lensectomy, two of them with retention of the posterior lens capsule.

The clinical development was monitored by means of slit-lamp examination, ophthalmoscopy, and measurement of intraocular pressure. The animals in the two groups were killed after three and six weeks and after three and six months respectively and the

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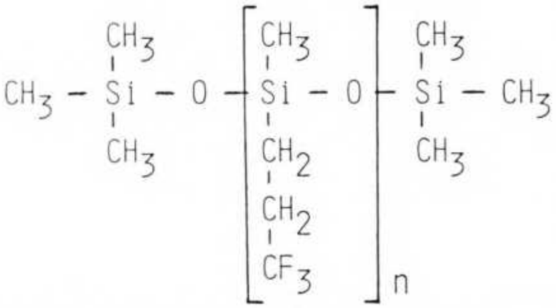

$$CH_3-\underset{CH_3}{\overset{CH_3}{Si}}-O-\left[\underset{CH_2CH_2CF_3}{\overset{CH_3}{Si}}-O\right]_n-\underset{CH_3}{\overset{CH_3}{Si}}-CH_3$$

Fig. 1 *Polytrifluoropropylmethylsiloxane. Viscosity (25°C) mPa s, 5000. Average chain length approximately 50. Average molecular weight approximately 7800. Refractive index (25°C) 1·38. Density (25°C) g/cm^3 1·29. Volatility 24 h 150°C ≤0·1%.*

eyes prepared for histological examination by gross examination and light microscopy.

Results

CLINICAL COURSE

The postoperative clinical course (Table 1) in all eyes filled with silicone oil was quite similar. The intraocular inflammation, with mixed conjunctival congestion and Tyndall phenomenon in the anterior chamber, decreased during the first three weeks and continued to decrease in the following weeks. Two control eyes, one with low specific gravity oil and one without silicone oil, were lost during the first six weeks owing to increasing inflammation and accompanying intraocular pressure rise due to secondary glaucoma, which showed no evidence of being related to the silicone oil.

A silicone bubble reached the anterior chamber in all eyes in which the lens capsule had been removed. The bubble diameter in the anterior chamber was ⅓ to ⅔ of the corneal diameter and remained stable. The bubble was located at the inferior and superior limbus for high and low gravity silicone oil respectively (Figs. 2, 3). From about the fifth day after silicone oil injection all eyes showed varying degrees of central keratopathy, characterised by central opacification and thickening of the corneal stroma, but no staining with topical fluorescein (Fig. 4). However, this central keratopathy decreased in all eyes and was no longer present in any eye after six weeks. This type of central keratopathy was identical in the two eyes filled with PDMS; in contrast no keratopathy was observed in the two control eyes without any silicone oil.

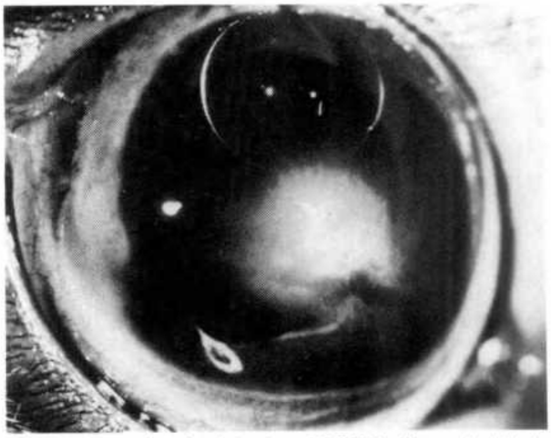

Fig. 2 *Six weeks after injection of PDMS, silicone bubble in superior part of anterior chamber. Central opacification of cornea with stromal thickening.*

Table 1 *Clinical course of eyes under investigation*

	Trifluorosiloxan						*Polydimethylsiloxan*				*Control*			
Posterior lens capsule	*3 weeks*		*6 weeks*		*3 months*		*6 months*		*3 weeks*	*6 weeks*	*3 weeks*	*6 weeks*	*3 months*	*6 months*
	intact	*removed*	*intact*	*removed*	*intact*	*removed*	*intact*	*removed*	*removed*	*removed*	*removed*	*removed*	*removed*	*removed*
Total number of eyes	4	11	4	10	4	8	3	3	2	2	5	4	4	3
Central keratopathy	4	11	—	6	—	—	—	2	2	2	—	—	—	—
Neovascularisation starting from the inferior limbus	—	—	—	2	—	5	—	2	—	—	—	—	—	—
Intraocular pressure	—	—	—	—	1	1	1	—	—	—	1 Secondary glaucoma, enucleation		1 Endophthalmitis, enucleation	

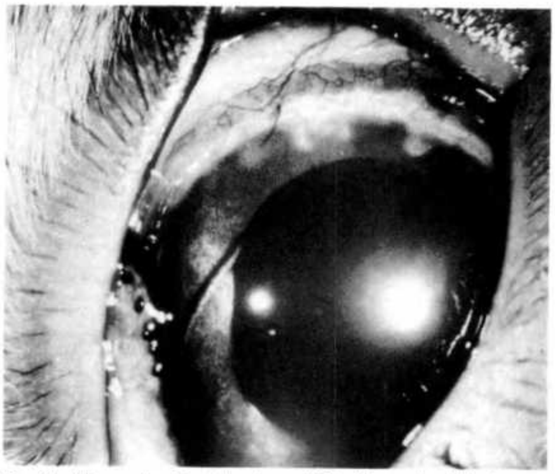

Fig. 3 *Six weeks after injection of FS, silicone bubble in inferior part of anterior chamber, light opacification of central cornea.*

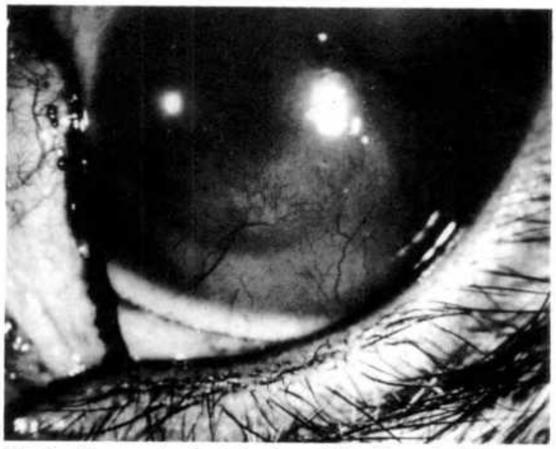

Fig. 5 *Six months after injection of FS, silicone bubble in inferior part of anterior chamber, superficial neovascularisation of inferior cornea.*

After six weeks two eyes began to develop clinically visible corneal neovascularisation from the inferior limbus. After three months five eyes showed this neovascularisation. Even after six months two out of three eyes having silicone oil in the anterior chamber displayed this type of neovascularisation (Fig. 5). Two eyes, one with the posterior lens capsule intact and the other with it removed, developed an increase of intraocular pressure which we could control by local application of betablockers. Two of the three eyes with intact posterior capsule showed no sequelae of the silicone oil in the anterior segment.

None of the 15 eyes showed any clinical signs of so-called emulsification or any side effects in the vitreous cavity, on the retina or on the disc.

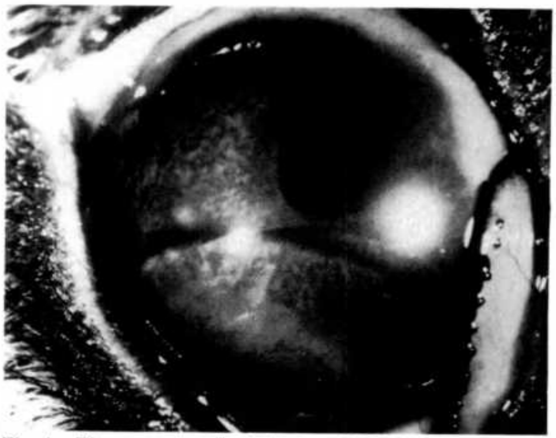

Fig. 4 *Three months after injection of FS, silicone bubble in inferior part of anterior chamber, central corneal opacification almost disappeared.*

HISTOPATHOLOGICAL RESULTS

Tissue responses, as detected by light microscopy, were observed at the corneal stroma and endothelium, on the iris surface and stroma, and to a minimal degree in the vitreous cavity. These tissue responses varied with the duration of the observation time and were much more pronounced in eyes filled with FS than in the control eyes filled with PDMS (Table 2).

The *central corneal opacity* noted clinically during the first six weeks of observation was unaccompanied by major histopathological changes except for possible mild stromal oedema.

Other *corneal stromal changes* were confined to the inferior cornea and were seen only in those eyes in which the lens capsule was defective and silicone oil had gained access to the anterior chamber of the eye. These eyes displayed a round cell infiltration and corneal stromal neovascularisation very early after silicone oil injection at the inferior cornea, where silicone oil was in contact with the endothelium. This corneal neovascularisation and round cell infiltration decreased in intensity after three months of observation. No corneal stromal thinning was observed in any of the eyes filled with silicone oil.

The *corneal endothelium* displayed a slightly increasing amount of cell loss during the observation period, confined mainly to the area of silicone oil contact and the area of limbal incision. Further, an increasing amount of endothelial silicone oil phagocytosis was seen the longer the observation period

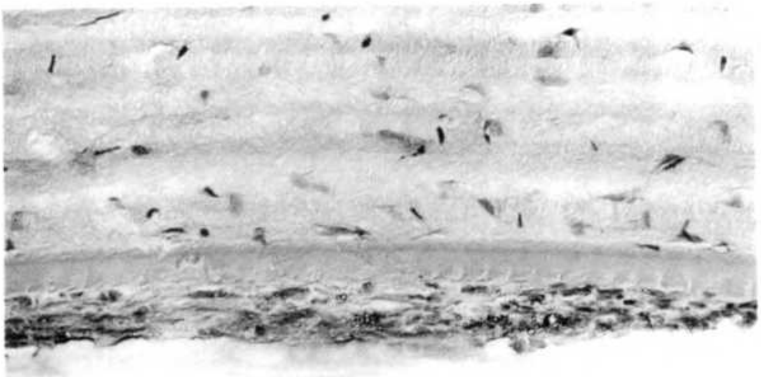

Fig. 6 *Posterior corneal fibrous tissue layer with many interspersed and phagocytosed silicone globules. Cornea of rabbit eye filled with FS and having a silicone oil bubble within the anterior chamber. Follow-up three months.*

went on. With the passage of time a moderate to marked retrocorneal fibrous tissue layer with phagocytosed silicone globules developed which was more pronounced at the superior border of the silicone oil bubble (Fig. 6).

The most prominent findings were observed at the *iris*. All eyes with FS displayed some oil droplets within the iris stroma. This reaction was observed also in eyes in which silicone had gained no access to the anterior chamber. Especially remarkable was the presence of a fibrous tissue layer on the anterior surface of the iris. It contained phagocytosed oil droplets similar to a foreign body reaction (Fig. 7a, b). This tissue response increased with time and appeared to be confined to the inferior iris leaflet, which was in contact with the heavy silicone oil. This tissue response was also observed in those cases where the lens capsule was left in place (Fig. 7c).

The *vitreous, retina, and optic nerve* displayed almost no tissue reaction even after six months. The only finding of any note was the presence of some macrophages on the retinal surface containing various amounts of clear spaces, presumably silicone droplets. No fibrocellular proliferation or tissue impregnation by silicone oil was observed.

When *control eyes were filled with PDMS*, with silicone oil at the superior part of the anterior chamber, they were observed for six weeks only. They showed less tissue response than those eyes filled with FS, which were examined after the same observation time, and displayed only minimal inflammatory reaction in the corneal stroma and no corneal neo-

Table 2 *Grading of tissue reaction of trifluorosiloxan and polydimethylsiloxan in control eyes as observed histopathologically*

	Trifluorosiloxan				*Poly-dimethyl-siloxan*	*Control eyes*
	6 weeks	*3 months*	*6 months*		*6 weeks*	*Without silicone oil*
			Lens capsule			
			Defective	*Intact*		
Corneal stroma, round cell infiltration of peripheral stroma	+	++	+	+/−	+/−	+/−
Neovascularisation	+	+	+/−	−	−	−
Corneal endothelium silicone phagocytosis	−	+	+	−	−	−
Rarefactation of endothelial cell layer	+/−	+	+	−	+/−	+/−
Retrocorneal fibrous tissue layer	−	+/−	++	−	−	+/−
Iris, silicone droplets in stroma	+/−	++	++	++	−	−
Fibrocellular membrane on anterior iris surface:						
without oil droplets				+/−		
with oil droplets	+	++	++		+/−	−
Vitreous macrophages containing silicone droplets	−	+	+	+	−	−
Retina and optic nerve tissue impregnation	−	−	−	−	−	−

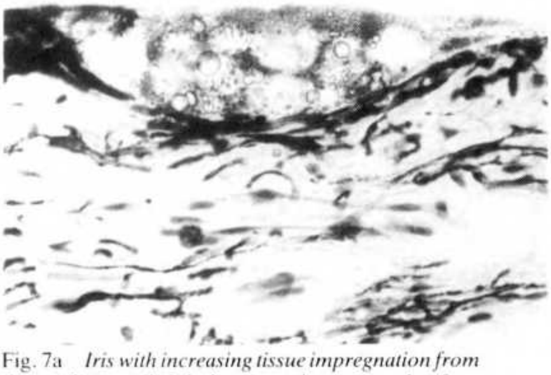

Fig. 7a *Iris with increasing tissue impregnation from fluorosilicone oil globules. As early as six weeks after intraocular application of FS marked aggregation of silicone globules surrounded by macrophages are seen on the iris surface.*

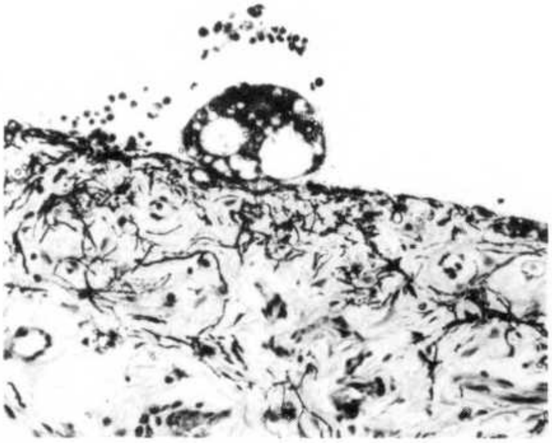

Fig. 7b *After three months of observation smaller globules are present also within the iris stroma.*

vascularisation. No oil droplets were observed within the tissues. However, the anterior surface of the iris was also covered by a comparatively discrete inflammatory membrane.

Control eyes without any silicone oil displayed a mild amount of endothelial cell loss and various degrees of retrocorneal fibrous tissue located primarily in the superior part of the cornea close to the limbal incision site. Only a very mild round cell infiltration was observed at the limbus.

Discussion

CHEMICAL AND PHYSICAL PROPERTIES OF FS

The molecule of FS is similar to that of PDMS, but with one methyl group replaced by a trifluorpropyl group in each dimethylsiloxane unit. This causes a higher molecular weight of the siloxane unit (MW=156) than that of PDMS (MW=74). However, the FS, with a viscosity of 5000 mPa s has an average chain length of only about 50 siloxane units and an average molecular weight of about 7800. In comparison PDMS with the same viscosity reaches a chain length of about 400 siloxane units and so a higher average molecular weight of about 30 000. This may in part be responsible for the different tissue reaction observed and discussed later.

The main difference between FS and PDMS is the former's higher specific gravity, which is also higher than that of the intraocular fluid. This may offer some advantages in clinical use. Recently it has become clear that entirely filling the eye with silicone oil can lead to complications such as glaucoma and keratopathy. Incomplete filling, however, leads to some accumulation of fluid. In the case of low specific gravity oil this fluid accumulates under the tamponade, whereas the use of a high specific gravity material would lead to accumulation of fluid above. If the location of the intraocular fluid pocket coincides with the location of the retinal tear, an occlusion of the subretinal space is not accomplished, and this can lead to redetachment.

A second advantage is the greater technical ease of silicone oil injection and endodrainage in cases of giant retinal tears and selected cases of trauma, since

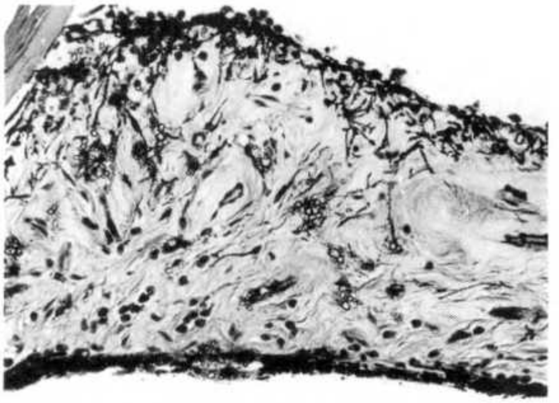

Fig. 7c *After six months iris tissue is markedly invaded by FS globules although the lens capsule was intact in this eye.*

heavy silicone oil sinks down to the posterior pole during an operation, so that it is unnecessary to make an endodrainage hole at the posterior pole.

The refractive index of FS is less than that of PDMS, which means that iatrogenic hyperopia after silicone oil filling is much less than that with PDMS. On the other hand the surface of the FS bubble is much more difficult to detect during the operation than that of PDMS.

TISSUE REACTION TO FS

Clinically a rather mild reaction to all types of silicone oil was observed. Whereas the transient central corneal stroma oedema was not confined to the area of contact between the silicone oil and the corneal endothelium, the more marked round cell infiltration and neovascularisation of the peripheral corneal stroma was confined to silicone-endothelial contact. The same was true for the iris tissue changes, such as tissue infiltration by FS droplets and silicone-containing fibrocellular membranes on the anterior iris surface.

Although these reactions are seen in the areas of direct contact between silicone and tissue layers, it is not quite clear whether they are merely mechanical or to some extent physicochemical in nature. The fact that after only six weeks the tissue reaction to FS was much more prominent than to PDMS points towards differences in reactions to various types of silicone oil. However, more comparative studies are needed to judge the significance of different reactions to various types of silicone oil.

Despite these differences in reactions in our experimental series, the extent of corneal changes observed in the rabbit eyes filled with FS was certainly less than that noted by Sternberg and associates.[6] We saw no corneal stromal thinning in areas overlying the silicone oil bubble.

Histologically the most prominent pathological changes due to FS in our series were observed in the iris tissue. Whether this formation of fibrocellular membranes at the anterior iris surface, the phagocytosis of silicone oil droplets, and the marked tissue impregnation are of clinical importance is still unclear.

In contrast to the rather alarming reaction to silicone oil in the anterior chamber of the eye, the reaction within the vitreous cavity was minimal and very similar to what we have observed when using purified PDMS in human eyes.[5] But in assessing changes in the anterior segment of the rabbit eyes one must take into consideration the fact that rabbits always have a much more pronounced reaction to any kind of ocular trauma than humans.

At present, in view of these findings, we consider the use of intraocular FS not to be justified until FS with better chemical and physical properties becomes available.

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Ocular findings in linear sebaceous naevus syndrome

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SUMMARY The case of a 5-month-old black female child with a linear sebaceous naevus syndrome and multiple congenital anomalies is presented. Ocular malformations consisted of colobomatous changes of the lid and retina, dermoid of the conjunctiva, chorioretinal changes, and peripapillary atrophy of the optic nerve. Systemic findings included midline cleft of the secondary palate with involvement by the naevus, bilateral hearing loss, asymmetrical skull bones, ventricular septal defect, epidermal inclusion cyst, and developmental delay without seizures.

Jadassohn[1] in 1895 was the first to employ the term organoid naevus as a distinct entity from pigmented naevi. In 1932 Robinson[2] surveyed the literature and introduced the term 'naevus sebaceus of Jadassohn'. Feuerstien and Mims[3] defined a new neurocutaneous syndrome in 1962 consisting of the triad of linear sebaceous naevus, convulsions, and mental retardation. Neurocutaneous syndromes include congenital lesions of the skin and of the central nervous system and often involve ocular and visceral malformations. Tuberous sclerosis, neurofibromatosis, Sturge-Weber disease, and von Hippel-Lindau disease all fall under the domain of neurocutaneous syndromes which are all ectodermal dysplasias.[4]

More recent cases expanded the scope of symptoms encountered in the new neurocutaneous syndrome. Marden and Venters[5] presented a case study showing that mesodermal malformations could be involved in the new neurocutaneous syndrome. Anomalies in their patient included severe failure to thrive, hydrocephalus, colobomas of the irides and choroid, lipodermoids, slanting of the auricle, multiple naevi, coarctation of the aorta, skull deformities, and the triad of linear sebaceous naevus, mental retardation, and seizures. Moynahan and Wolff[6] further expanded the possible symptoms associated with the linear sebaceous naevus. They described a patient who had a linear sebaceous naevus, generalised EEG irregularities, skull asymmetry, conjunctival lipodermoids, and cortical atrophy of the right hemisphere as indicated by transillumination over the right frontal region of the skull.

The following case provides an interesting constellation of findings and helps to illustrate both common features and variations encountered in the linear sebaceous naevus syndrome.

Case report

A 5½-month-old female child was referred because of failure to thrive and multiple congenital anomalies. She weighed 7 pounds 12 ounces (3515 g) at birth after a normal spontaneous vaginal delivery without complications.

Immediately on examination a midline, vertical, hyperpigmented, papular lesion extending from the anterior fontanelle to the upper lip was noted. Similar lesions were present over the cheeks, left ear, chest, left arm, and neck extending down the back (Fig. 1). Irregular areas of hyperpigmentation were noted on the lower limbs. The patient was also noted to have a midline palatal cleft of the secondary palate, and a soft tissue mass encroaching on the temporal limbus in the left eye. There was no family history of any neurological or dermatological disease.

PHYSICAL EXAMINATION

On admission the child was a cachectic, weak infant. Anthropomorphic measurements were: head circumference 39·5 cm (<5% percentile), length 55 cm (<5% percentile), and weight 3·72 kg (<5% percentile). There was slight asymmetry of the skull on the right side. On auscultation of the chest a regular rate and rhythm with a II/VI systolic ejection murmur heard best at the left lower sternal border was noted. A 2×2 cm midline mass was located 1 cm below the umbilicus. Neurological examination

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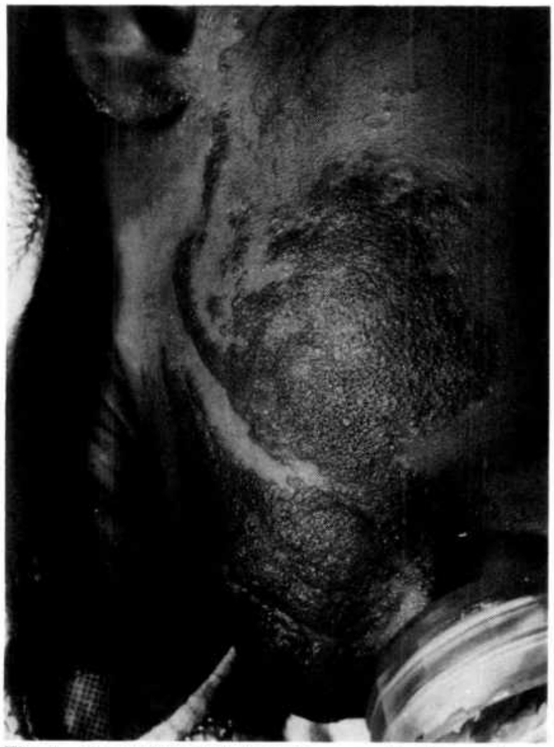

Fig. 1 *Hyperpigmented skin lesion present on face and lower jaw of 5½-month-old female child.*

revealed decreased tone throughout, without focal neurological findings.

OCULAR EXAMINATION

Visual acuity appeared to be normal in both eyes, though the child showed a preference for the right eye. The pupils were equal, round, and reactive to light. The extraocular movements were within normal limits in both eyes. External examination revealed a circumferential yellow, lipoid-like subconjunctival deposit encroaching on the temporal limbus of the left eye. In addition a coloboma of the right upper lid was evident (Fig. 2). Funduscopic examination of the left eye showed a choroidal and disc coloboma with chorioretinal changes. Examination of the right fundus revealed peripapillary atrophy of the disc also with chorioretinal changes.

LABORATORY DATA

The haemoglobin was 12·1 g/dl and the packed cell volume was 36·9%, with a white blood cell count of $11{\cdot}7\times10^{9}$/l. A random blood glucose test gave 65 g/dl (3·6 mmol/l); the blood urea nitrogen value was 9 g/dl (1·5 mmol/l). It was also determined that the patient had a normal female karyotype.

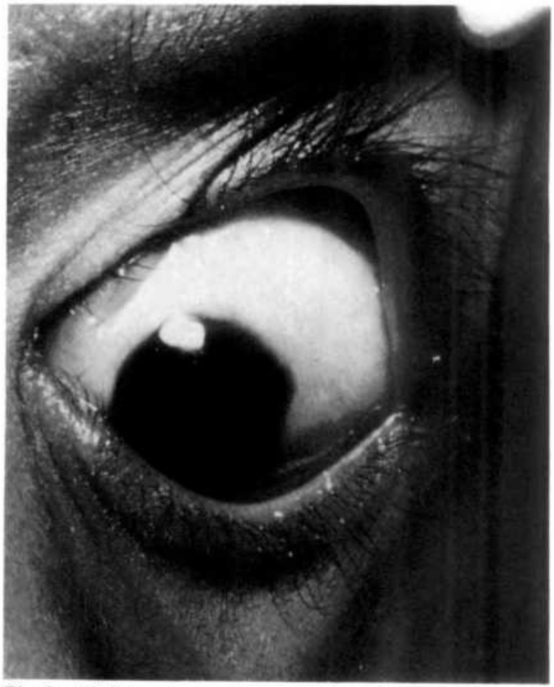

Fig. 2 *Midline naevus sebaceus with ocular involvement of the lid and bulbar conjunctiva.*

Skull x-ray showed minimal asymmetry of the skull on the right side, with a suggestion of some asymmetry of the sphenoid bone on the left side. A bone scan of the skull was performed to help rule out craniosynostosis. It proved negative. An electroencephalogram showed evidence of voltage asymmetry, with the presence of suspicious slowing over the left hemisphere that was non-specific in nature.

A chest x-ray showed a slight boot shaped heart with an uptilted apex suggestive of right ventricular hypertrophy. The electrocardiogram showed some right ventricular hypertrophy. M-mode and TT echocardiograms revealed a small ventricular septal defect with slight poststenotic aortic dilatation. A filling defect in the pharynx, which was later found to be a redundant uvula, a partial malrotation of the jejunum, and a small sliding oesophageal hernia were visualised during a gastrointestinal x-ray examination.

Tympanometry was performed and showed type B changes bilaterally. A brain stem evoked response showed conductive hearing loss bilaterally with possible mixed changes, particularly on the right side.

SURGICAL PROCEDURES

The patient underwent conjunctival biopsy, biopsy of the abdominal lesion near the umbilicus, placement

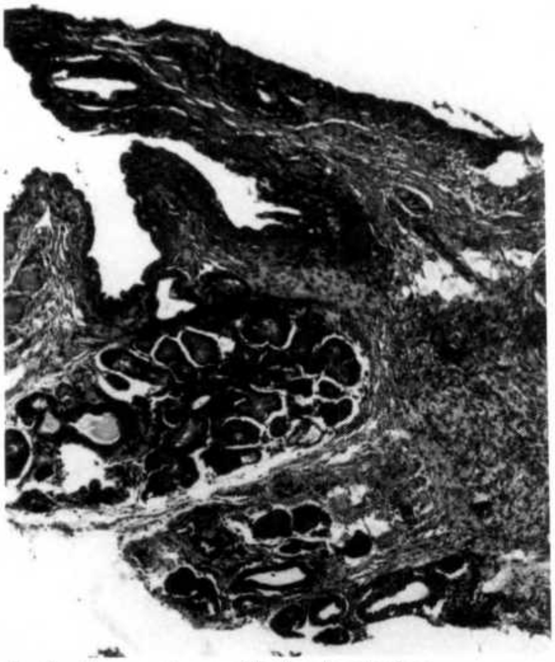

Fig. 3 *Naevus sebaceus of Jadassohn showing hyperkeratosis, acanthosis, and hypertrophied sebaceous gland in the superficial corium. H and E.*

of pressure equalising tubes, and intervelar veloplasty with palatoplasty utilising redundant uvula. At the time of surgery it was noted that the naevus appeared to involve the upper lip, the entire soft palate, and the right buccal mucosa. The bifid uvula was thickened and enlarged as well as elongated. Histological examination of the conjunctival biopsy revealed a dermoid. The biopsy of the uvula proved to be a squamous papilloma, and examination of the abdominal biopsy showed an epidermal cyst. During this same admission to hospital a histopathological analysis was also made of the skin lesion, which showed sebaceous gland hyperplasia consistent with a sebaceous naevus (Fig. 3).

One and one-half years after discharge from hospital the child has not had a seizure, but she still appears to be developmentally delayed according to the primary care physician.

Discussion

Mehregan and Pinkus[7] reviewed 150 cases of organoid naevus which consisted mostly of the type designated naevus sebaceus of Jadassohn. Their analysis provides a description of the life history and a discussion of the malignant quality of the lesion. The first phase of the life history involves under-development of hairs and sebaceous glands. The second phase, occurring at the time of puberty, is characterised by massive development of sebaceous glands, papillomatous epidermal hyperplasia, and maturation of apocrine glands. The final stage is heralded by the development of benign and malignant naevoid tumours. Fifty-two tumours developed within the organoid nevi in 33 patients. The distribution was as follows: basal-cell epithelioma (21), syringadenoma papilliferum (8), solid hidradenoma (6), infundibuloma (5), sebaceous epithelioma (4), apocrine cystadenoma (4), and keratoacanthoma (4).

Table 1 *Associated findings in linear sebaceous naevus syndrome*

External disease
Lipodermoid of upper lid[8]
Unilateral ptosis[8]
Coloboma of upper lid[*]
Anterior segment disease
Lipodermoids (unilateral and bilateral) of conjunctiva[5 12*]
Vascularisation of cornea[5]
Coloboma of iris[5]
Corneoscleral mass (lacrimal and cartilage choristoma)[10]
Intrascleral cartilage and bone[10]
Cataract[10]
Posterior segment disease
Retinal degeneration with chorioretinal coloboma[5]
Retinal detachment with rosette formation[10]
Peripapillary atrophy[10*]
Coloboma of optic disc
Others
Nystagmus[5]
External oculomotor nerve palsy with pupillary 'sparring'[8]
Cortical blindness[9]
Esotropia[11]

[*] Our case.

Solomon[8] appears to have coined the name 'epidermal naevus syndrome' in reporting 44 patients, many with the findings of naevus sebaceus of Jadassohn: 71% of his patients had skeletal anomalies, 46% had central nervous system (CNS) abnormalities, and 38% had both.

Many ocular findings have been described in association with linear sebaceous naevus syndrome (Table 1). They include colobomas of the lid, epibulbar lipodermoids, bulbar dermoids with pannus formation, iris and chorioretinal colobomas, generalised retinal degeneration, antimongoloid lid fissures, asymmetry of orbital bones, peripapillary ectasia of the sclera, and esotropia.[9] In 1972, Haslam and associates[9] presented a case of unilateral external oculomotor nerve palsy with pupillary sparing. Lansky *et al.*[10] in that same year published a case of linear sebaceous naevus syndrome in association with cortical blindness. Bilateral Coats' disease was identified in a 4-year-old girl with ichthyosis hystrix, a variant of the epidermal naevus syndrome. Burch *et al.*[11] suggested a possible relation between this finding and other vascular abnormalities and malfunctions seen in this syndrome. In 1981 Wilkes *et al.*[12] reported a case of a 13-year-old boy who had an ipsilateral facial sebaceous naevus in association with a left corneoscleral limbal mass composed of lacrimal tissue and cartilage, together with intrascleral cartilage and bone. Retinal detachment and rosette formation were present on the left, while the findings in the right eye were a myopic crescent, peripapillary atrophy, and a colobomatous defect of the optic disc.

Our patient appeared to have normal visual acuity with a left temporal conjunctival dermoid, coloboma of the retina and disc, and chorioretinal changes. The right eye had a coloboma of the upper lid, peripapillary atrophy of the disc, and chorioretinal changes.

No race, sex, ethnic, familial, or predisposing factors are known to be associated with the syndrome.[10] As in this case the appearance of the syndrome is a sporadic event with no clear inheritance pattern. An exception is a case reported by Bianchine[13] of a patient with the new neurocutaneous syndrome who had a familial history of convulsions and mental deficiency.

Patients often have asymmetry of the sphenoid bones.[8] Additional cranial anomalies include widening of the sella, hydrocephalus, hemimacrocephaly, and unilateral ventricular widening.[14] Lansky and coworkers[10] discussed the association of cutaneous manifestations ipsilateral to the abnormal encephalographic focus. This patient's electroencephalogram revealed voltage asymmetry with diffuse slowing over the left hemisphere of a suspicious nature. The most common EEG finding involves focal and multifocal spiking, with other EEG tracings described.[15] Herbst and Cohen[16] first reported an association of a typical hypsarrythmic pattern with the linear sebaceous naevus. This type of pattern generally indicates a diffuse brain lesion according to the authors.

The new neurocutaneous syndrome involves the triad of linear sebaceous naevus, mental retardation, and seizures. The typical cutaneous lesions (circumscribed, firm, flat, yellow plaques with smooth, furrowed surfaces) and mental retardation (developmental delay), but not seizure activity, characterised our patient. This case represents a forme fruste of the syndrome. Other variants of the new neurocutaneous syndrome have been described. Lantis and associates[17] discussed two cases of linear sebaceous naevus which did not have the triad. Their patients had ocular dermoids, linear sebaceous naevus, coloboma of the eyelid, and abnormal skull *x*-rays; however, neither patient was mentally retarded or had experienced seizure activity.

The clinical outcome in linear sebaceous naevus syndrome is usually not fulminant. However, Mollica *et al.*[15] presented a case of a newborn baby with neurological symptoms and extensive malformations, including angiomas of the scalp, lipodermoids of the conjunctiva, adenoma of the liver, horseshoe kidney, patent ductus arteriosus, and diffuse epidermal naevus. The baby died 36 hours post partum. At necropsy a large leptomeningeal haemagioma was found in the middle fossa, with associated intraventricular and ependymal haemorrhage. The authors suggested that the neurological symptoms of the linear sebaceous naevus syndrome may be the result of hamartomatous lesions of the CNS.

Armed with the knowledge of the life history and the associated anomalies the physician is better equipped to diagnose and treat the linear sebaceous naevus syndrome. Our case demonstrated several characteristic features and the newly recognised association of a midline cleft of the secondary palate with extensive naevus involvement of the buccal mucosa and a bifid uvula.

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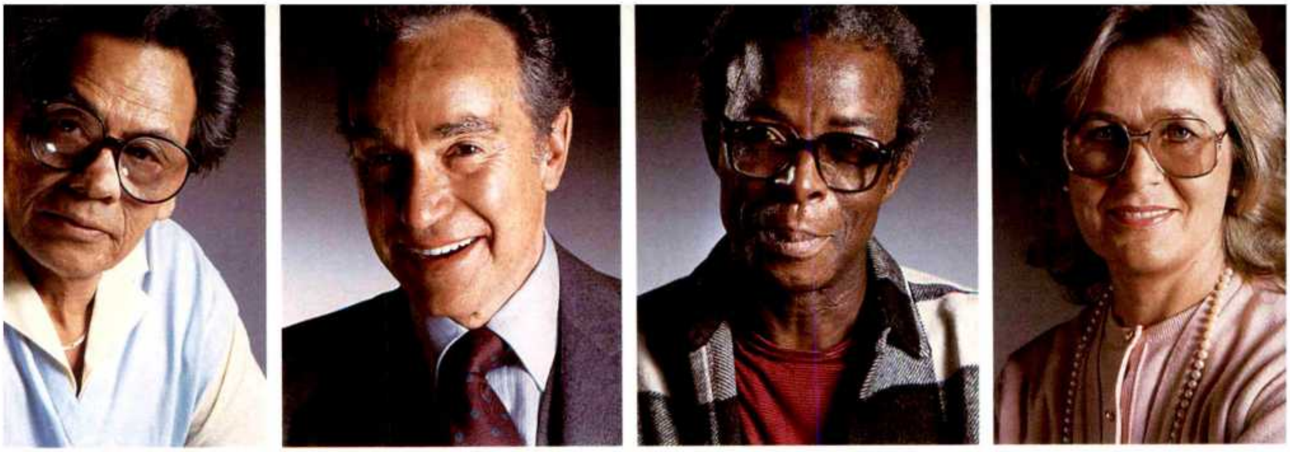

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Responses to tuberculin in the guinea-pig eye as a model of cell mediated immune responses in the external eye

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SUMMARY The clinical and histological findings in an animal model of ocular cell mediated immune responses are described. These were evoked in sensitised guinea-pigs by dropping tuberculin into the conjunctival sac or injecting it under the palpebral conjunctiva. When tuberculin was dropped into the conjunctival sac, higher doses were required to evoke a strong response than when it was injected subconjunctivally. When high doses of antigen were used for challenge, a mild response was observed in unchallenged contralateral eyes. The cellular response at low doses of tuberculin consisted predominantly of mononuclear cells. At higher doses the cellular infiltrate was more pronounced, and polymorphonuclear cells tended to predominate 24 hours after challenge, while at 48 hours mononuclear cells predominated.

It has been suggested that cell mediated immune responses are important in the pathogenesis of eye diseases including trachoma, herpes simplex virus infection, chronic staphylococcal infection, and vernal keratoconjunctivitis. However, there is as yet little direct evidence to support this hypothesis. Most in-vivo studies of cell mediated immune responses have been carried out in the skin, and there are relatively few studies in other tissues. We have developed an animal model using tuberculin to study cell mediated responses in the outer eye in the absence of infection or immediate-type reactions. This is similar to the diagnostic test in humans, introduced in 1909, in which tuberculin in saline or petroleum jelly was instilled into the conjunctival sac and ocular reactions were observed.[1] Previous studies of the reaction to tuberculin in the guinea-pig eye have involved injection of tuberculin into the guinea-pig cornea.[2-4] In our model, briefly described in an earlier paper,[5] guinea-pigs sensitised to tuberculin are challenged by dropping antigen on to the conjunctival sac or injecting it into the palpebral conjunctiva. We here report further studies on this model.

Material and methods

Animals. Female albino guinea-pigs of the Dunkin-Hartley strain weighing 250 to 500 g were used.

Antigens. Freund's complete adjuvant was used for sensitisation (Bacto Adjuvant Complete (H27Ra), Difco Laboratories); tuberculin, mammalian purified protein derivative (PPD) of tuberculin, or human PPD, lyophilised and phenol-free, was used for challenge (Ministry of Agriculture, Fisheries and Food, Central Veterinary Laboratories, Weybridge, Surrey).

Sensitisation. Animals were sensitised with four simultaneous intradermal injections of 0·2 ml of a 50/50 v/v emulsion of Freund's complete adjuvant in phosphate buffered saline. Animals were skin-tested five to 10 weeks after sensitisation, and only animals with induration of at least 18 mm diameter were chosen for eye challenge.

Ocular challenge. Right eyes were challenged by one of two methods: (1) mammalian PPD (0·02 ml) was instilled into the conjunctival sac and the lids closed with gentle massage to distribute the antigen; (2) human phenol-free PPD (2 μg in 0·01 ml) was injected subconjunctivally midway in the upper palpebral conjunctiva of the right eye with a 30 g needle. Eyes were examined and were removed for histological examinations at various times after challenge.

Clinical examination. The methods of clinical examination of the conjunctiva and cornea were as described previously.[6] Eyes were examined 4, 8, 18, 24, and 48 hours after challenge.

Histological examination. The methods used for

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histological examination were as described previously.[7]

Results

CLINICAL FINDINGS

Challenge with drops of PPD

Sensitised and control animals with clinically normal eyes were challenged in the conjunctival sac of the right eye with drops containing 0·004, 0·04, 0·4, 4·0, or 40 µg of mammalian PPD. No inflammatory responses were observed at any time in the eyes of unsensitised control animals. In sensitised animals there were no inflammatory responses four and eight hours after challenge.

At 24 hours three of 10 animals challenged with 0·004 µg and all 10 animals challenged with 0·04 µg PPD showed slight hyperaemia of the right palpebral conjunctiva, but at 48 hours all these eyes appeared normal.

At 18 hours three out of five animals challenged with 0·4 µg PPD and all animals challenged with 4·0 µg PPD showed mild hyperaemia of the right palpebral conjunctiva, and at 24 hours all animals had mild hyperaemia and oedema of the palpebral conjunctiva and mild erythema of the right lid margin. Mild hyperaemia and oedema of the bulbar conjunctiva were observed at 24 and 48 hours in the animals challenged with 4 µg PPD, but there was no bulbar response in the animals challenged with 0·4 µg PPD. At 72 hours all eyes appeared normal.

All animals challenged with 40 µg PPD showed mild to moderate hyperaemia and oedema of the palpebral and bulbar conjunctiva, slight congestion of limbal vessels, erythema of lid margins, and mucoid discharge at 18, 24, and 48 hours. At 72 hours the intensity of these clinical signs had diminished. At 72 hours five guinea-pigs were killed for histological examination and the lids of the right eyes shaved before dissection. After shaving, the eyelid skin was seen to be moderately erythematous. At five days there was only mild hyperaemia of the palpebral conjunctiva, and, after shaving, the skin of the right eyelids was seen to be slightly bruised in appearance. At seven days all eyes appeared normal, but the skin of the right eyelids still appeared slightly bruised when shaved.

The left (unchallenged) eyes of about half of the animals challenged with 0·4 µg PPD or more had mild hyperaemia of the palpebral conjunctiva at 24 hours.

Challenge with drops of PPD after mild trauma to the conjunctiva

Five guinea-pigs were challenged with 4 µg PPD in the conjunctival sac of the right eye immediately after the upper palpebral conjunctiva had been rubbed firmly several times with a cotton wool swab. At four hours there was mild hyperaemia of the upper palpebral conjunctiva, which had disappeared at eight hours. The clinical findings at 24 and 48 hours were the same as in eyes which had been challenged without swabbing.

Secondary challenge with drops of PPD

Five guinea-pigs which had been challenged 10 days previously were rechallenged with 4 µg PPD in the same eye. The inflammatory responses in the 48 hours following challenge were very similar to those seen in animals given a primary challenge with 4 µg PPD.

Challenge with subconjunctival injection of PPD

Guinea-pigs were challenged in the right eye. In unsensitised animals there was mild hyperaemia of the right upper palpebral conjunctiva at four and eight hours, while the left eyes were normal. At 24 hours all eyes were normal. When sensitised animals were challenged, there was mild hyperaemia of the upper palpebral conjunctiva at four hours, but at eight hours all eyes appeared normal. At 18, 24, and 48 hours there was moderate to severe oedema and erythema of the lid margins and purulent discharge at the site of injection. There was mild to moderate hyperaemia and severe oedema of the palpebral conjunctiva, and mild to moderate hyperaemia and oedema of the bulbar conjunctiva, with mild to moderate limbal oedema and congestion of limbal vessels and mild stromal keratitis. The left, unchallenged eyes, had mild hyperaemia and oedema of the palpebral conjunctiva, and some had mild oedema of the bulbar conjunctiva at 24 hours, but at 48 hours the left eyes appeared normal. At 24 hours some animals were killed for histological examination. When the eyelids were shaved the right eyelids showed severe oedema and erythema, while the left eyelids were normal in appearance. At 72 hours right eyelids were moderately erythematous, and at five days the skin of the lids appeared to be slightly bruised.

HISTOLOGICAL FINDINGS

Challenge with drops of PPD

No significant histological changes were seen at 24 or 48 hours in any of the eyes of animals challenged with 0·004 or 0·04 µg PPD. In some eyes challenged with 0·4 µg PPD there were small patches of mononuclear cells infiltrating the conjunctival epithelium near the lid margins and in and under the palpebral conjunctival epithelium.

In most eyes challenged with 4 µg PPD there were groups of mononuclear cells with a few polymorphonuclear cells in all parts of the palpebral conjunctiva

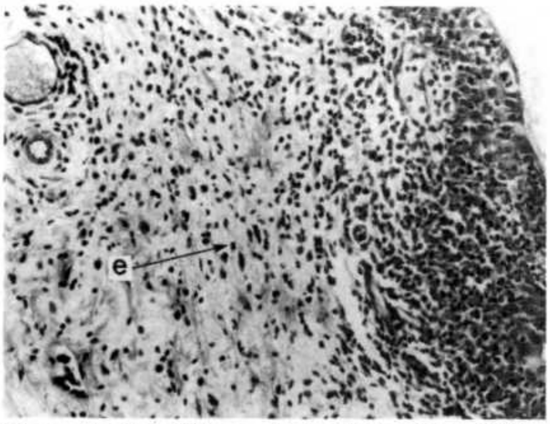


Fig. 1 *Reaction at 24 hours after instillation of 40 μg PPD into the conjunctival sac. Palpebral conjunctival epithelium with polymorphonuclear cells and submucosa with a predominantly mononuclear cell infiltrate and a few eosinophils* (e).

and the lid margins. In some eyes there was a mild cellular infiltrate throughout the palpebral conjunctiva and the lid margins, which consisted of mononuclear cells with a few polymorphonuclear cells, and there was also a mild mononuclear cell exudate in the conjunctival sac. In the bulbar conjunctiva there were a subepithelial mononuclear cell infiltrate and some polymorphonuclear cells, mainly in the epithelium. In all eyes the limbal region had a marked cellular infiltrate, consisting of mononuclear cells with only a few polymorphonuclear cells in or just under the epithelium. At 48 hours the histological appearance was very similar to that at 24 hours. Five days after challenge some eyes still had small groups of mononuclear cells in the submucosa, with a few scattered plasma cells. There were no significant changes in left, unchallenged eyes.

After challenge with 40 μg PPD most eyes showed a moderate to heavy mixed cellular infiltrate, with many polymorphonuclear cells in the conjunctival epithelium, a predominantly mononuclear cell infiltrate in the submucosa, and vascular dilatation (Fig. 1). The limbus generally showed a moderate, predominantly mononuclear cell infiltrate with some polymorphonuclear cells and eosinophils and occasional plasma cells, and enlargement of limbal vessels (Fig. 2). Some left, unchallenged eyes had small patches of mononuclear cells, but most appeared normal.

Challenge with subconjunctival injection of PPD

At 24 hours after challenge several eyes showed a mild to moderate cellular infiltrate under the epidermis of the skin of the eyelids, in which mononuclear cells predominated. Some eyes had a heavy polymorphonuclear cell infiltrate in the epithelium of the palpebral conjunctiva close to the lid margin with consequent loss of structure. In these eyes a polymorphonuclear cell exudate was also present (Fig. 3). The submucosa showed dilated and congested vessels, and a predominantly polymorphonuclear cell infiltrate in the loose connective tissue, but not in the adjacent muscle (Fig. 3). Other eyes showed only a very few polymorphonuclear cells in the lid margin epithelium and a predominantly mononuclear cell infiltrate of the submucosa. Eosinophils were also usually present, but numbers varied considerably. The upper palpebral conjunctiva usually had a heavy

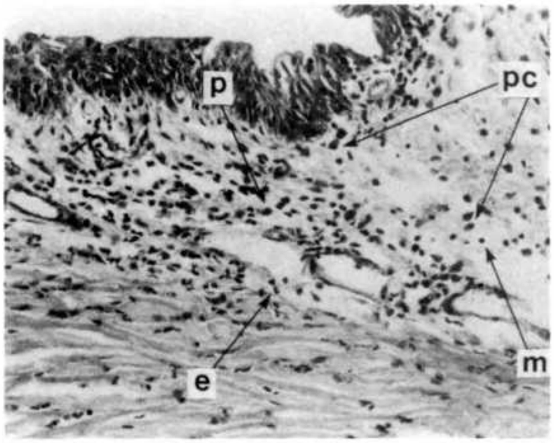


Fig. 2 *Reaction at 24 hours after instillation of 40 μg PPD into the conjunctival sac. Limbus with mixed cellular infiltrate consisting of mononuclear cells* (m), *polymorphs* (p), *eosinophils* (e), *and plasma cells* (pc).

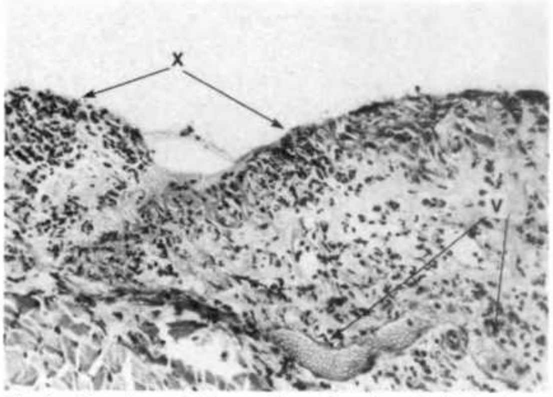


Fig. 3 *Reaction at 24 hours after subconjunctival injection of 2 μg PPD. Palpebral conjunctiva showing polymorphonuclear cell infiltrate with loss of structure in epithelium near lid margin; congested vessels* (v), *and a polymorphonuclear cell exudate* (x).

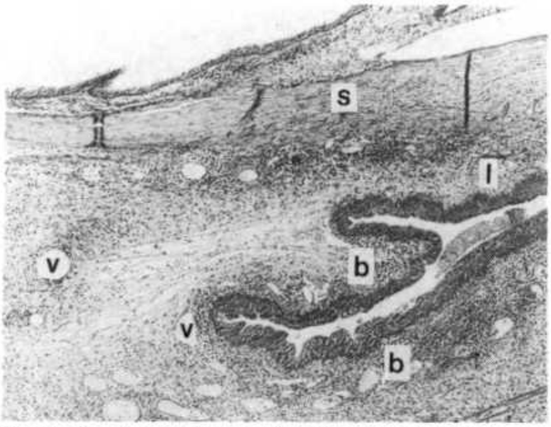


Fig. 4 *Reaction at 24 hours after subconjunctival injection of 2 µg PPD. Marked cellular infiltration of the bulbar conjunctiva* (b), *limbus* (l) *and sclera* (s), *and diluted vessels* (v).

mixed cellular infiltrate under the epithelium, while the deeper tissues had a predominantly mononuclear cell infiltrate. In the lower palpebral conjunctiva most eyes had only a mild infiltrate with some polymorphonuclear cells in the epithelium, and a few mononuclear cells and eosinophils in the submucosa. In most eyes the bulbar conjunctiva had a moderate mixed cellular infiltrate in the submucosa, with a few polymorphonuclear cells in the epithelium, while a few eyes had a heavy mixed cellular infiltrate in the bulbar conjunctiva and limbus with dilated and congested vessels.

In one eye the episcleral tissue under the bulbar conjunctiva, and the underlying sclera adjacent to the limbus, the pars plana, and ciliary body all had a heavy mixed cellular infiltrate. The corneal stroma of this eye also had a heavy mixed cellular infiltrate (Figs. 4, 5).

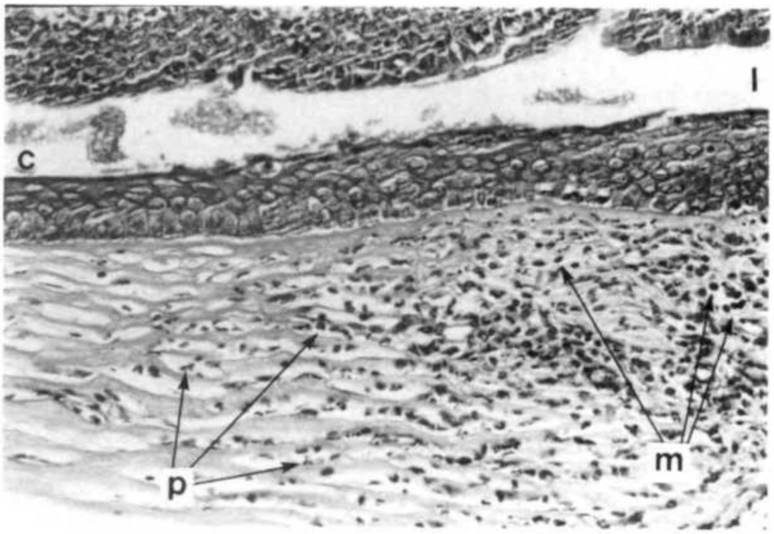
At three, five, and seven days there was a steady diminution of the cellular infiltrate in most areas of the conjunctiva. Polymorphonuclear cells disappeared more rapidly than mononuclear cells. At seven days several eyes had small patches of cells in the palpebral conjunctiva and limbus consisting of mononuclear cells, including a few plasma cells.

Most unchallenged left eyes showed only mild mononuclear cell infiltration in the palpebral conjunctiva at 24 and 48 hours.

Discussion

We have extended our earlier studies of immune responses to PPD in the guinea-pig external eye. We have found that the maximal inflammatory response occurs 18 to 48 hours after challenge by instillation of drops or subconjunctival injection of PPD. There was a steady decline in intensity 48 hours after challenge. The timing is similar to that of guinea-pig skin reactions, which are maximal at 24 hours.[8] In studies of cell mediated immune responses in the cornea the challenge has usually been carried out by injecting antigen into the cornea.[2,4,9,11] We have shown that this traumatic procedure is unnecessary. Ocular responses can be evoked by injecting the antigen into the palpebral conjunctiva, or by dropping it into the conjunctival sac, although we found that higher doses of PPD were required to evoke a strong response when it was dropped on to the conjunctiva than when it was injected subconjunctiv-

Fig. 5 *Reaction at 24 hours after subconjunctival infection of 2 µg PPD, showing limbus* (l) *with a predominantly mononuclear cell infiltrate* (m), *and cornea* (c) *with a mainly polymorphonuclear cell infiltrate* (p).



ally. The responses we observed in the palpebral and bulbar conjunctivae are similar to those reported in the limbus of animals which had been challenged by intracorneal injection, which at about 24 hours had a limbal cellular infiltrate consisting predominantly of polymorphonuclear cells.[2,4,9,11] Thus we can conclude that ocular cell mediated immune responses to tuberculin in the guinea-pig eye are accompanied by a mixed polymorphonuclear and mononuclear cell response, whatever routine of challenge is used. In addition we regularly found some eosinophils, which confirms a previous report.[11] However, there were major differences in the corneal responses which we observed compared with those of animals challenged by intracorneal injection. This is because of the damage caused by the intracorneal injection and the presence of an antigen depot in the cornea.

A heavy mixed cellular infiltrate was found in the cornea, episcleral tissue, sclera, and anterior uvea of one animal after subconjunctival injection of PPD. It was similar to naturally occurring sclerokeratitis associated with granulomatous infection, rheumatoid arthritis, and several autoimmune disorders. Silverstein and Zimmerman described a similar reaction in guinea-pigs after intravitreal injection of tuberculin, with a mixed cell infiltrate in the cornea and limbus. However, in their animals the choroid, sclera, and episclera had a predominantly mononuclear cell infiltrate.[12]

A mild clinical and histological response was observed in unchallenged left eyes, particularly when higher doses of PPD were dropped into the conjunctival sac, or when it was injected. It is possible that interocular transfer of antigen may have occurred. It has been demonstrated in rabbits that subconjunctival injection of radiolabelled human serum albumin in one eye is followed by the appearance of radioactivity in the other eye. Most of this transfer does not involve the blood circulation, and it has been suggested that the major pathway is the lymphatic system.[13]

Our main reason for studying responses to PPD in the eye is because it is likely that cell mediated immune responses are important in ocular herpes simplex virus and chlamydial infections. However, during infection the agent is multiplying, and many immune and inflammatory responses are occurring at the same time. There are, however, some similarities between the guinea-pig ocular response to PPD and to reinfection with guinea-pig inclusion conjunctivitis (GPIC) agent *(Chlamydia psittaci)*. In both the cellular response consists of polymorphonuclear and mononuclear cells, with a few eosinophils. We have argued that the response to reinfection with GPIC agent is predominantly cell mediated because the number of mononuclear cells present is much larger than in primary GPIC agent infection, and the number of polymorphonuclear cells is very much reduced.[14] In addition, since intradermal injection of live GPIC agent evokes a cell mediated immune response in the skin, it seems reasonable to expect that live GPIC agent in the eye should also evoke an ocular cell mediated reaction. However, there are differences in the dose response curves of the eye and skin; much larger doses are needed to evoke skin responses than with eye responses.[15] It is now known this is also true for skin and eye responses.

This model of ocular responses to PPD has allowed us to study the features of cell mediated immune responses in the eye. This will enable us to recognise these reactions during infection and in other conditions, when they may be present along with other immune and inflammatory reactions.

We thank Professors Barrie Jones and John L Turk for advice, Mary Lang, Eileen Wilson, and Maria Pink for technical assistance, and the Medical Research Council for financial support.

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Orbital involvement with desmoplastic melanoma*

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SUMMARY A 79-year-old woman developed an orbital mass five and a half years after excision of a cutaneous melanoma from the side of the nose. The initial orbital biopsy was interpreted histopathologically as a malignant fibrous histiocytoma, but special stains and electron microscopy showed it to be a desmoplastic malignant melanoma which had apparently spread to the orbit from the prior skin lesion by neurotropic mechanisms. The occurrence of a desmoplastic neurotropic melanoma in the orbit has not been previously recognised. The problems in the clinical and pathological diagnosis of this rare type of melanoma are discussed.

Orbital involvement with malignant melanoma most often occurs secondary to extrascleral extension of posterior uveal melanoma.[1] Primary orbital melanoma and metastatic cutaneous melanoma to the orbit are extremely rare.[2] Desmoplastic melanoma is a rare form of cutaneous melanoma which can extend from a superficial location into the deep reticular dermis by neurotropic mechanisms.[3,4] We report a unique case of desmoplastic melanoma in which such a tumour extended from the nasal skin into the deep orbit, clinically simulating a primary orbital tumour.

Case report

A 79-year-old white woman was referred to the Oncology Service at Wills Eye Hospital in April 1985 because of a two-month history of proptosis, blepharoptosis, and blurred vision in the left eye. The patient gave a history of having had a 'basal cell carcinoma' removed from the left side of her nose in December 1979, followed by a repeat biopsy and a definitive wide surgical excision. She was subsequently involved in an automobile accident and suffered fractures of the left orbital floor and zygoma. In August 1984 she had excision of scar tissue around the left eye and biopsy of a 'cyst' in the left upper eyelid, which was diagnosed at another hospital as a malignant fibrous histiocytoma.

A general physical examination gave essentially normal results, and complete examination of the right eye revealed no abnormalities. Examination of the left eye disclosed diffuse thickening of the periocular skin and upper eyelid with 2 mm of proptosis and 4 mm of blepharoptosis (Fig. 1). There was mild

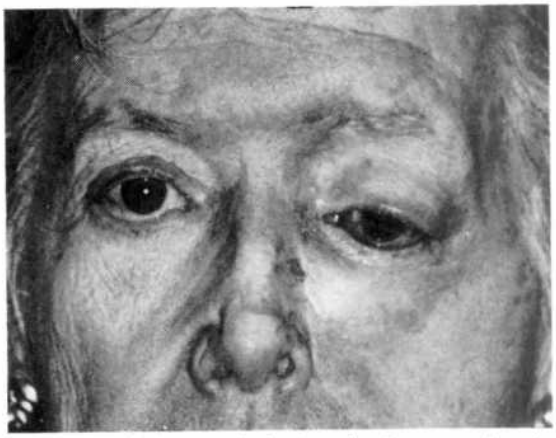

Fig. 1 *Facial photograph of patient showing proptosis and blepharoptosis on the left side.*

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*Presented at the Annual Meeting of the Eastern Ophthalmic Pathology Society, St Thomas, Virgin Islands, 1 November 1985.

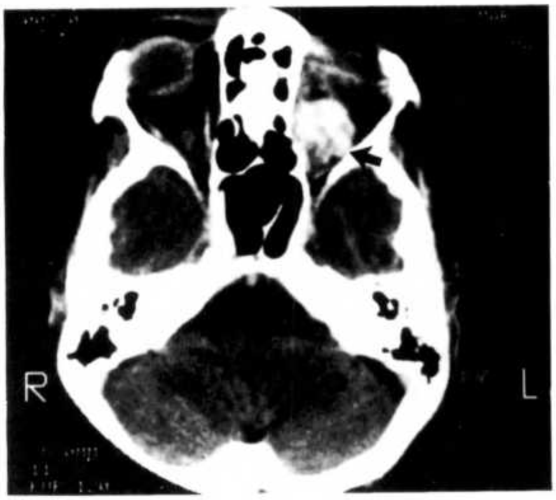

Fig. 2A

Fig. 2 *Computed tomography showing irregular but fairly well circumscribed left orbital mass (arrow)* A: *Axial view.* B: *Coronal view.*

scarring on the left side of the nose where the 'basal cell carcinoma' was previously excised.

Computed tomography (CT) of the orbits showed a large irregular mass filling most of the left orbit superonasally and posteriorly (Figs. 2A, B). It appeared to extend to the orbital apex but showed no evidence of bone destruction.

In view of the patient's history and clinical findings the initial differential diagnosis included orbital recurrence of basal cell carcinoma, orbital recurrence of malignant fibrous histiocytoma, or possible granulomatous inflammation related to prior trauma. The histopathological sections of the prior skin biopsies were requested.

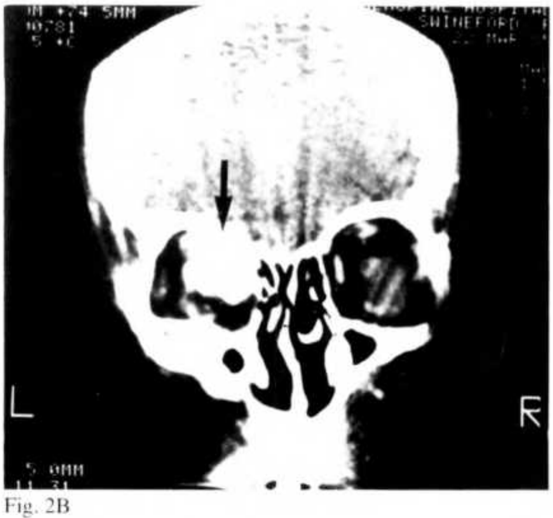

Fig. 2B

It was elected to perform a biopsy of the orbital mass to determine which of the three diagnostic possibilities was correct. Therefore an incisional biopsy of the mass was performed by way of a superonasal brow incision and extraperiosteal approach. A wedge biopsy was taken from the anterior portion of a firm white orbital mass, and no attempt was made to excise it completely. Tissue submitted for routine frozen sections during surgery showed malignant spindle cells with considerable extracellular material. On frozen sections the specimen was interpreted as a malignant spindle cell tumour, most likely a malignant fibrous histiocytoma.

The permanent sections disclosed interlacing bundles of spindle cells with pleomorphic hyperchromatic nuclei, sometimes arranged in a storiform (closely packed in cartwheel) pattern, sometimes with a foamy-appearing cytoplasm (see discussion of pathology, below). The preliminary diagnosis was recurrent malignant fibrous histiocytoma of the left orbit. On the day after surgery a copy of the pathology report of the prior biopsy of the left eyebrow was received, and it also indicated a diagnosis of malignant fibrous histiocytoma.

On the following day we received word that the patient had been seen in consultation by the Pigmented Lesion Group at the University of Pennsylvania in December 1979. To our surprise the nasal skin lesion had been interpreted as lentigo maligna melanoma. Because the lesion had extended close to the surgical margins, a course of radiotherapy, giving 4920 rad over a 22-day period, had been administered. The revised diagnosis by the Pigmented Lesion Group was not indicated on our report from the other hospital, which still reflected the diagnosis of malignant fibrous histiocytoma.

In view of this new information the biopsy of the left upper eyelid and the orbital biopsy were reassessed. Both biopsies were finally diagnosed as a desmoplastic neurotropic melanoma (see following discussion on pathology). The patient was readmitted to the hospital and underwent an orbital exenteration with removal of the medial canthal area and upper eyelid. She is alive and well 14 months after our initial examination.

PATHOLOGY

A review of the initial shave biopsy of the original lesion from the left side of the nose demonstrated increased numbers of atypical melanocytes in the basal layers of the epidermis with evident desmoplasia in the dermis (Fig. 3). The areas of desmoplasia contained scattered atypical spindle shaped

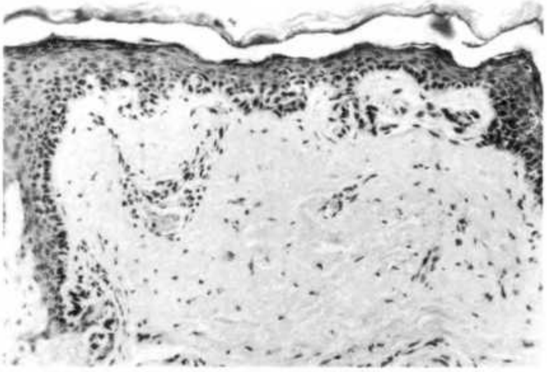

Fig. 3 *Photomicrograph of the original cutaneous lesion from the nose showing atypical melanocytes at the basal layer of the epidermis, consistent with the radial growth phase of lentigo maligna melanoma. Note the actinic elastosis in the superficial dermis. Haematoxylin-eosin.*

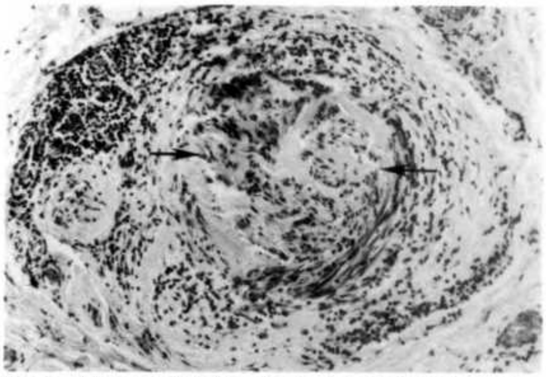

Fig. 5 *More detail of dermal nerve from primary tumour, showing permeation of endoneurium and perineurium by cytologically atypical spindle cells (neurotropism) (arrows). Haematoxylin-eosin.*

melanocytes which exhibited perineural and endoneural involvement in the subcutaneous connective tissues (Figs. 4 and 5). The diagnosis was lentigo maligna melanoma with a neurotropic desmoplastic reaction.

The orbital biopsy and the subsequent orbital exenteration specimen showed the tumour to be composed of fascicles and cords of atypical spindle cells with a marked desmoplastic reaction identical to that seen in the cutaneous tumour (Fig. 6A). In some areas the cells resembled fibroblasts, with rather uniform nuclei, while in other areas the nuclei showed considerable pleomorphism with a vesicular appearance and prominent nucleoli (Fig. 6B). Particularly near the margins of the specimen there was perineural and sometimes intraneural invasion by the spindle tumour cells. Fontana stains for melanin were negative. The S-100 protein stain was positive in many of the tumour cells (Fig. 7).

The orbital lesion was processed for routine electron microscopy. The tumour was composed of spindle shaped fibroblast-like cells with abundant rough endoplasmic reticulum. Although some of the cells were void of melanosomes, a number of them contained spheroidal granular melanosomes, typical of poorly differentiated melanosomes seen in many melanomas (Fig. 8).

The final diagnosis was orbital metastasis of desmoplastic neurotropic melanoma arising from cutaneous lentigo maligna melanoma.

Discussion

Desmoplastic malignant melanoma is a rare variant of cutaneous spindle cell melanoma which was first

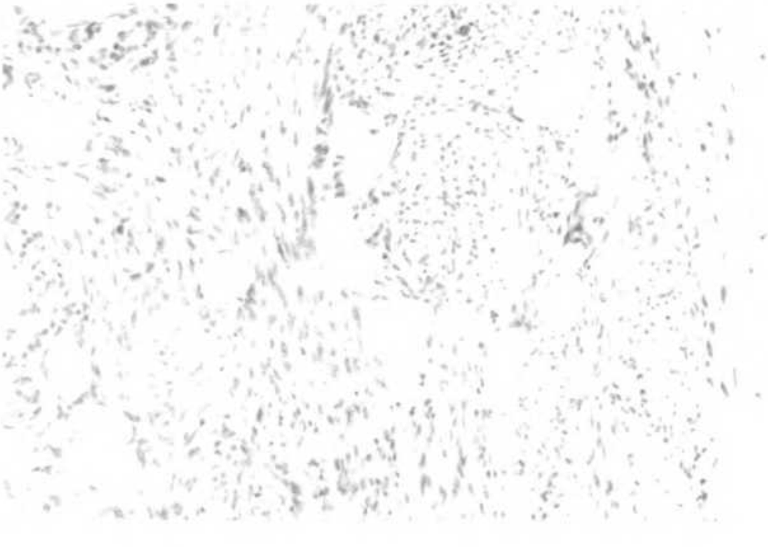

Fig. 4 *Photomicrograph of subcutaneous tissues deep to skin lesion showing perineural invasion by atypical melanocytes and infiltration of subcutaneous fat by a spindle cell tumour with a fibrous stroma, characteristic of a desmoplastic and neurotropic melanoma. Haematoxylin-eosin.*

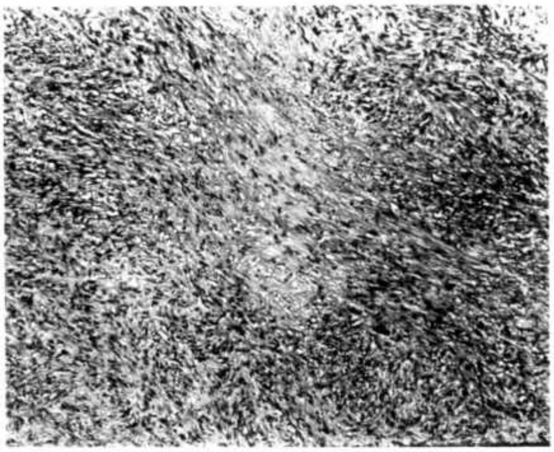

Fig. 6A

Fig. 6 *Photomicrograph of orbital mass showing haphazardly arranged malignant spindle cells with desmoplastic reaction. Haematoxylin-eosin.* A: ×*20.* B: ×*125.*

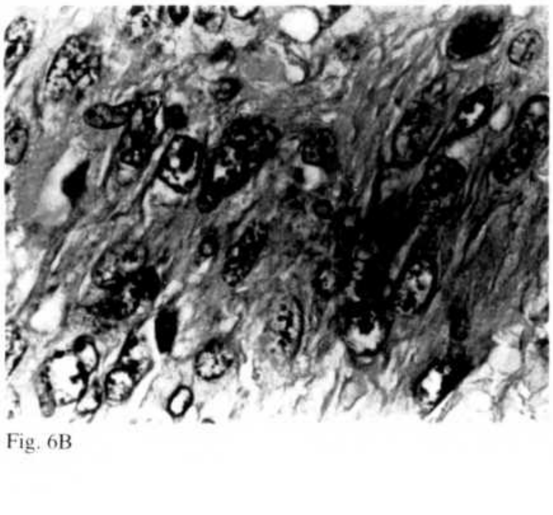

Fig. 6B

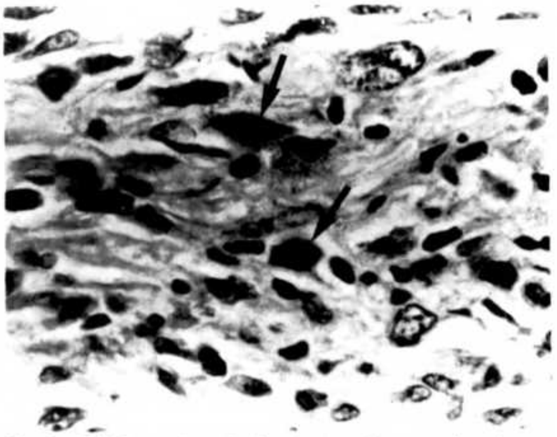

Fig. 7 *S-100 protein stain showing positive cytoplasmic staining in tumour cells (arrows).*

described by Conley and associates in 1971.[14] In addition to their seven original cases about 25 other cases have been reported.[5-17] Most reported cases have been in the head and neck region, with one case involving the eyelid.[12] The case reported here is apparently the first to have deep orbital involvement and to produce ipsilateral proptosis.

The typical evolution of a desmoplastic melanoma is now relatively clear. Most reported cases have been preceded by a lentiginous or (less often) by a superficial spreading melanoma in the face or neck region. The skin lesions often appeared innocuous clinically and were not usually interpreted microscopically as being highly malignant, because the desmoplastic and neurotropic components in the deep reticular dermis were overlooked on microscopic examination.

Approximately six months to two years after excision of the initial lesion the patient characteristically develops a slowly enlarging, firm, subcutaneous mass deep to the site of the primary lesion. Biopsy of the recurrent (or persistent) lesion demonstrates bundles of atypical spindle cells with varying degrees of malignancy and marked desmoplasia. Neurotropism of the tumour is often observed.[14 16 17] Melanin pigment often cannot be demonstrated in the deeper lesion, even with special stains and electron microscopy, though it is usually evident in the initial cutaneous lesion even by routine light microscopy. A few desmoplastic melanomas have been completely amelanotic, though they show intradermal patterns otherwise characteristic of melanoma.

The recurrent deeper lesion is often misdiagnosed histopathologically as fibrosarcoma, fibromatosis, scar tissue, or (as in our case) fibrous histiocytoma.[4] In our case the Fontana-Masson stain for melanin was negative, but the use of immunoperoxidase stains and electron microscopy were helpful in establishing the diagnosis. Stains for S-100 protein were positive (Fig. 7), suggesting a tumour of neural crest origin, and electron microscopy showed spheroidal granular melanosomes in the cytoplasm of the tumour cells. These features, combined with the history of a prior cutaneous melanoma, strongly supported the diagnosis of melanoma, in spite of the fact that the diagnosis was less evident with routine light microscopy.

The mechanism of orbital spread in our case can be deduced from the histopathology and from a review of the literature on desmoplastic melanomas. Both in the original skin lesion and in the orbital recurrence

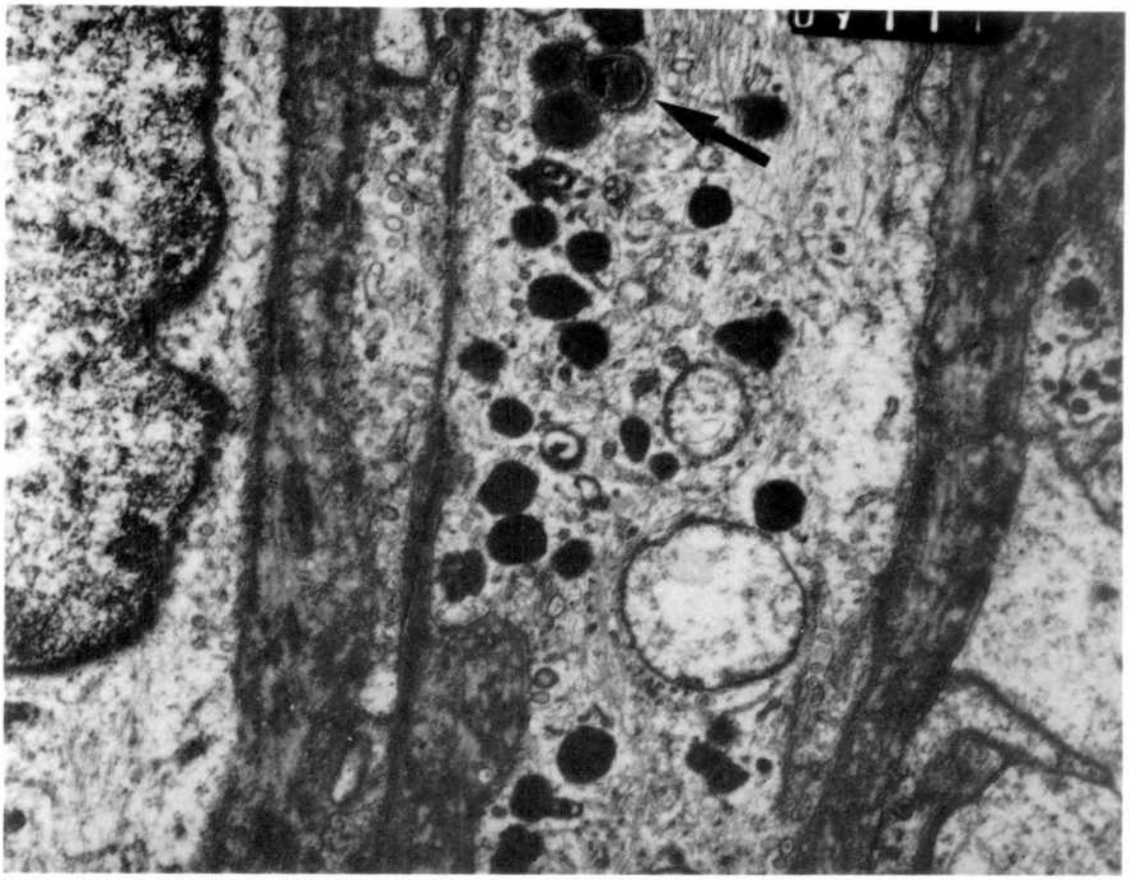

Fig. 8 *Electron photomicrograph of the orbital tumour showing spheroidal granular melanosomes within cytoplasm of tumour cell (arrow). ×10 000.*

there was marked perineural and intraneural involvement by tumour cells. It is recognised that the rare case of melanoma which shows neurotropism has a tendency toward desmoplasia (stimulation of fibrosis).[13] It is most likely that the neurotropic tendency of our patient's tumour was responsible for spread of the tumour cells along peripheral nerves into the orbit, where they proliferated as a solid mass. This would be consistent with other reported cases, where the deeper nodule seemed to occur from neural spread of the melanoma to a deeper location. Review of the earlier biopsies in such circumstances may reveal tumour within nerves at the margin of the specimen, as was found in our case.

The most important considerations in the differential diagnosis of an eyelid mass with secondary orbital involvement are basal cell carcinoma and sebaceous gland carcinoma. The majority of such cases are basal cell carcinomas which have been neglected or inadequately excised. Sebaceous gland carcinomas also have a marked tendency to invade the orbit, particularly the fossa of the lacrimal gland, where they can simulate a primary lacrimal gland tumour.[18] Malignant melanomas of the eyelid are rare and generally do not secondarily invade the orbit. However, certain cases of lentiginous or superficial spreading melanomas have a tendency to neurotropism. When located in the eyelid area such neurotropic melanomas can easily invade the orbit and simulate a primary orbital tumour, as occurred in our case. In such cases biopsy of the orbital mass may disclose an amelanotic spindle cell tumour which is not at first glance similar to the original skin lesion.

The desmoplastic variety of melanoma should be considered in the differential diagnosis of a spindle cell tumour of the orbit, especially if there has been a prior history of excision of a melanocytic tumour of the eyelid. In such cases a review of the original biopsy combined with the use of special stains and electron microscopy may be helpful in establishing the correct diagnosis.

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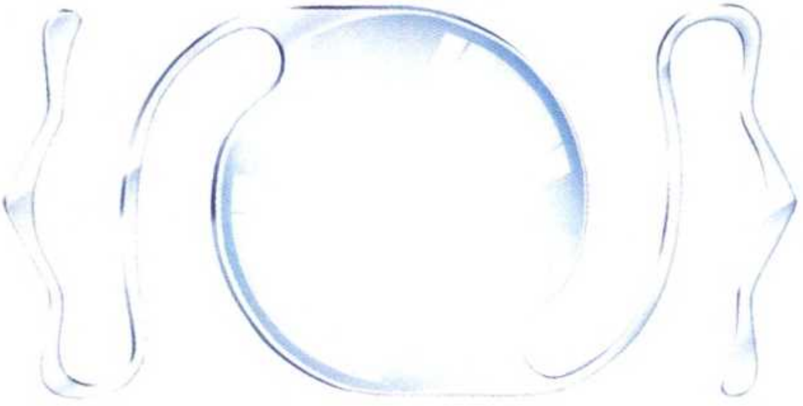

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British Journal of Ophthalmology, 1987, **71**, 285-289

Use of soft contact lenses in an eye casualty department for the primary treatment of traumatic corneal abrasions

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SUMMARY We have assessed the role of bandage contact lenses in the primary treatment of traumatic corneal abrasions. Patients treated with bandage lenses healed more quickly $(0\cdot05>p>0\cdot02)$ and with less discomfort $(0\cdot05>p>0\cdot02)$ than those treated traditionally, with the added advantage of maintaining vision during treatment. Resterilisation of contact lenses reduces the cost and makes the treatment economically viable. Large diameter lenses were fitted satisfactorily without the use of keratometry.

Traumatic corneal abrasions represent a substantial proportion of the problems presenting to the eye casualty department. In a recent three-month period at St Thomas's Hospital 120 (11%) out of 1086 new patients were treated for this common problem. Chiapella and Rosenthal[1] have recently reported a similar frequency of 848 (12·9%) out of 6576 patients seen in a year at Leicester Royal Infirmary. Each patient with this injury suffers marked short term discomfort and visual disability.

Traditionally the management of corneal abrasions consists of topical mydriatics, antibiotics, and pad and bandage. The healing period may last for several days and is associated with continuing pain and further visual disability from the dressing. Alternatively, ocular surface abnormalities can be successfully treated with bandage contact lenses, achieving the goals of pain reduction, facilitation epithelial healing, and proper surface hydration.[2] Moreover, visual function is retained. The secondary use of such lenses has been reported in cases of delayed healing of corneal abrasions or where damage to the basement membrane and Bowman's layer is associated with epithelial instability and recurrent erosions.[2] There have been no reported trials of the use of bandage lenses in the primary management of corneal abrasions, and this study sets out to show that patients with large surface area losses ($>4\ \text{mm}^2$) may benefit from this approach.

Material and methods

All patients seen in the eye casualty department at St Thomas's Hospital between 7 February and 20 July 1985 were considered. Twenty eight patients with traumatic abrasions were entered in a randomised controlled trial after fulfilling the following criteria: the abrasion was of a surface area of greater than $4\ \text{mm}^2$, the patient was over 18 years and under 65 years old, there was no evidence of secondary infection or retained foreign body or coincidental ocular pathology, and no previous treatment had been given. The area of abrasion was measured by the slit-lamp gated beam. No assessment of basement membrane damage was made.

Suitable patients were randomly allocated into one of two treatment groups: (*a*) occlusive pad and bandage, (*b*) bandage contact lens. All patients received guttae chloramphenicol 0·5% and homatropine 2%. Focus 80 0·16 mm centre thickness, 8·6 mm back central optic radius, 14·5 mm diameter, 80% water plano hydrophilic contact lenses were

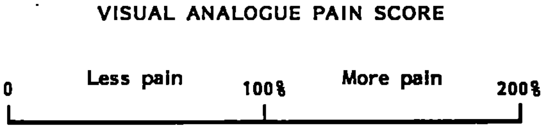

Fig. 1 *Patients were shown this figure and they marked the percentage of their pretreatment pain that they experienced after one day.*

Correspondence to D J Spalton.

Table 1 *Patients treated with pad and bandage*

Number	*Hours since injury*	*Age*	*Surface area of abrasion (mm^2)*	*Pain score on day 1 (%)*	*Days until healing*	*Mode of injury*	*Comments*
1	3	33	8	95	4	Grit in eye	
3	5	32	4	100	2	Poked finger in eye	
9	2	25	12	100	4	Baby poked finger in eye	Defaulted after three days
10	47	29	20	150	3	Sheet of paper in eye	Redundant corneal epithelium debrided at presentation. Returned after six days with minor recurrent abrasion
11	14	29	8	120	4	Baby poked finger in eye	Defaulted after three days
13	2	30	9	10	3	Floppy disc in eye	
16	6	47	4	25	3	Awoke with painful eye	
18	22	49	16	40	2	Baby poked finger in eye	Redundant corneal epithelium debrided
19	72	28	7	25	3	Baby poked finger in eye	
20	2	25	4	20	1	Cigarette in eye	
23	20	35	6	75	2	Foreign body in eye while hammering	Defaulted after one day
26	2	43	6	20	1	Baby poked finger in eye	
27	2	33	30	195	2	Awoke with painful eye	Redundant corneal epithelium debrided
28	50	28	18	25	2	Finger nail in eye	
Mean	17·79	33·28	10·86	71·43	2·57		
Standard deviation	21·77	7·43	7·33	55·11	0·98		
Standard error of mean	5·82	1·99	1·96	14·74	0·26		

used. They were applied without preliminary keratometry. The patients were reviewed daily and the abrasions considered healed when local punctate keratitis only could be observed on slit-lamp biomicroscopy of the injured site. Each day the patients made an assessment of their pain on a visual analogue scale (Fig. 1).

Results

These are summarised on Tables 1, 2, and 3, and in Figs. 2 and 3. The groups were compared by a two-tailed Student's t test. The patients in each treatment group were comparable with respect to age, time elapsed since injury, and size of abrasion ($0{\cdot}05>p>0{\cdot}1$). Those treated with a bandage lens noted less pain after 24 hours than those treated with a pad and bandage ($0{\cdot}05>p>0{\cdot}02$). They also reached the healing point more quickly ($0{\cdot}05>p>0{\cdot}02$). In the contact lens group patient no.6 could not tolerate a lens for more than 24 hours, by which time the abrasion had virtually healed, and had to be changed to a pad and bandage. Patient no.8 went for six days without reattending and has been excluded from the analysis.

In the pad and bandage treatment group patients 9, 11, and 23 all failed to attend for final review and discharge after daily attendances while the abrasions remained unhealed. It is assumed that these lesions had healed by the following day, but they might in fact have taken rather longer. In that case the difference between the average healing times of the two groups would have been more marked.

Discussion

After corneal epithelial injury there is a cellular response within 1–5 hours leading to infiltration by polymorphonuclear leucocytes and macrophages. The adjacent epithelium undergoes amoeboid transformation and cell division, and the defect may be covered within 24–48 hours. Epithelial stability requires the presence of an intact basement membrane, proper surface hydration, an absence of secondary infection, normal precorneal tear film function, and protection from further lid induced trauma during blinking.[2,3] Soft bandage contact lenses may offer these conditions more reliably than an occlusive dressing, just as they have already been shown to be helpful in the management of many corneal surface diseases and certain penetrating injuries.[3-5] However, Williams and Buckley have recently shown bandage lenses to be singularly unhelpful and possibly detrimental when compared with the topical application of oculentum simplex in the management of recurrent corneal erosions in map-dot-fingerprint dystrophy,[6] but they also suggest that trauma is of little importance in the production of erosions in this condition.

The study suggests that the primary treatment of

Table 2 *Patients treated with bandage contact lens*

Number	*Hours since injury*	*Age*	*Surface area of abrasion (mm²)*	*Pain score on day 1 (%)*	*Days until healing*	*Mode of injury*	*Comments*
2	0·75	27	8	25	2	Radio aerial in eye	
4	2	51	20	10	1	Punched in eye	
5	14	32	12	15	2	Fell off motorcycle	
6	11	28	34	75	3	Taking off makeup	Unable to tolerate bandage contact lens in spite of cornea virtually healing in one day; changed to chloramphenicol eye ointment and pad
7	14	25	5	70	2	Foreign body hitting eye	
8	29	67	6	?	?	Foreign body hitting eye	Failed to attend until telephoned and requested to return to casualty department
12	4	22	4	40	2	Plant leaf in eye	
14	4·5	76	48	30	2	Tear ducts syringed earlier in the day	Returned the next day with a recurrent abrasion
15	12	26	8	20	2	Punched in eye	Redundant corneal epithelium debrided before lens applied
17	29	36	4	10	1	Unknown	
21	4	44	28	10	2	Foreign body hitting eye	
22	23	33	9	50	2	Scratched in eye by dog's claw	Returned after two weeks with a minor recurrent corneal abrasion
24	26	42	16	50	1	Plaster in eye	
25	10	27	4	30	2	Pencil poked in eye	
Mean	12·95	38·28	14·71	33·46	1·85		
Standard deviation	9·46	15·77	12·90	21·34	0·53		
Standard error of mean	2·53	4·22	3·45	5·71 (n=13)	0·14 (n=13)		

traumatic corneal abrasions with soft contact lenses has an apparent advantage over the traditional occlusion in terms of reduced pain during healing and speedier healing. To this can be added the further advantage of faster rehabilitation; four of our patients were able to return to work with their lenses in situ. Possible disadvantages are seen from the patient who defaulted from follow-up with a contact

Table 3 *Statistical analysis of the results for the two treatment groups*

	Patients treated with pad+ bandage		*Patients treated with bandage contact lens*		*t*	*p*
	Mean	*Standard deviation*	*Mean*	*Standard deviation*		
Hours since injury	17·79	21·77	12·95	9·46	0·76	Not significant
Age	33·28	7·43	38·28	15·77	1·07	0·5>p>0·1
Surface area of abrasion	10·86	7·33	14·71	12·90	0·97	0·5>p>0·1
Pain score after 24 h of treatment	71·43	55·11	33·46	21·34	2·39	0·05>p>0·02
Days until healing	2·57	0·98	1·85	0·53	2·40	0·05>p>0·02

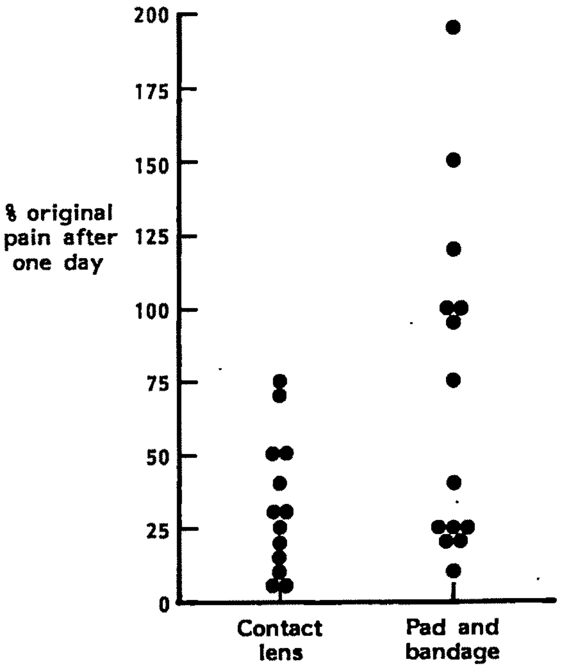

Fig. 2 *Pain score after one day.*

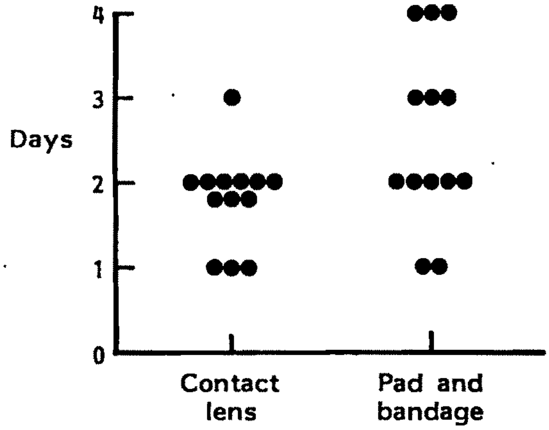

Fig. 3 *Number of days until healing.*

lens fitted (no.8). In this case there was no problem when he was seen and the lens removed six days later. However, the complications of prolonged usage are well known, and a patient who absconds with a lens in place may be at some risk.[2,7] In a series of 322 cases of ulcerative keratitis 56 (17%) were associated with the use of contact lenses, and of these 86% were soft lenses for the correction of ametropia.[8] Soft contact lenses are an important risk factor for the development of infected corneal ulcers, but traumatic abrasions are also a risk factor, and we believe that with properly sterilised and fitted bandage lenses, and with the use of a prophylactic broad spectrum antibiotic, the risks are minimal over such a short period of time. In most patients the abrasion healed within two days, after which the lens was removed.

The study further shows that fitting a bandage lens without complication can be undertaken by ophthalmic casualty medical staff without the use of keratometry or special training, provided a large back optic radius lens is used. The availability of a keratometer and specialised contact lens experience is beyond the scope of a routine ophthalmic casualty service. We explicitly set out to show that, with a careful choice of suitable lens and a clinical check for fit at the time of application, followed by short term therapeutic use, keratometry is unnecessary. Our findings bear this out, as poor fit was not a practical problem.

A further potential problem with bandage lenses is that of corneal hypoxia. The partial pressure of oxygen in the precorneal tear film is about 155 mmHg with the eyes open and falls to 55 mmHg on eyelid closure.[9,10] It falls further when the lids are closed and a soft lens is in place, to a level of 23 mmHg or below, and clinically significant corneal hypoxia may result.[9,10] It has been held that even lenses with a high oxygen permeability {DK of over 40 $(\text{cm}^2/\text{s})(\text{ml}O_2/\text{ml} \times \text{mmHg}) \times 10^{-11}$ (35°C)} and low centre thickness may approach this threshold. The Focus 80 lens has a DK of 48·6 $(\text{cm}^2/\text{s})(\text{ml}O_2/\text{ml} \times \text{mmHg}) \times 10^{-11}$ (35°C) and a centre thickness of 0·16 mm.[11] No problems of corneal oedema were observed in our patients and the risk of corneal hypoxia does not appear to be important. This is reflected in the increased healing of the abrasion in the soft lens group, possibly because these patients have greater oxygen exposure during the day, when their eyes are open, than those in the pad and bandage group, who may be relatively hypoxic all the time.

Limitations of the use of such treatment are the obvious ones of expense and availability of lenses. Each bandage lens costs £15 to the NHS compared with about £3 for three days' treatment with a pad and bandage. However, this is offset by the facts that these lenses may be resterilised either by heat or chemically,[11] and that fewer casualty attendances may be required of the patient and of the department's resources, so that the treatment may be more economical.

The limitations of this study are the relatively small number of patients, the four patients who failed to observe the follow-up protocol, the lack of data on the condition of the basement membrane and Bowman's layer at the time of initial assessment, and the lack of long-term follow-up to assess the problem of recurrent abrasions. Brown and Bron,[12] reviewing recurrent erosions, found a history of trauma in 56% of 80 patients, 65% of which occurred within four months of the original injury. However, no one to our knowledge has investigated prospectively the impact of primary treatment on this complication. We found that in the contact lens group two patients returned shortly after the healing point with recurrent erosions, one after only 24 hours and the other after 14 days. No such problems were noted with the pad and bandage group. We conclude that the results support the hypothesis that bandage contact lenses used in the primary treatment of traumatic corneal abrasions offer certain advantages over conventional treatment, namely a faster and more comfortable healing period at a reasonable economic cost.

We thank Mr M G Falcon for his advice during the preparation of this manuscript.

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Treatment of ptosis in chronic progressive external ophthalmoplegia

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SUMMARY Seventeen patients with ptosis as a feature of chronic progressive external ophthalmoplegia were managed in accordance with a new protocol. An anterior approach levator advancement was performed on seven patients (13 lids) with more than 4 mm of levator function and a brow suspension procedure on eight patients (14 lids) with minimal levator function, in whom the frontalis muscle was relatively spared. Ptosis props were prescribed for two patients with a very weak orbicularis and poor lid closure. Six patients required long term lubricants, and one developed a postoperative corneal abscess associated with a poor Bell's phenomenon. Satisfactory elevation of the lids was achieved in 16 patients (25 lids).

The surgeon's choice of operation for ptosis correction is normally based on the degree of ptosis and the amount of levator function.[1] However, in chronic progressive external ophthalmoplegia (CPEO) increasing weakness of the levator palpebrae superioris is accompanied by deterioration in function of the frontalis, orbicularis oculi, and external ocular muscles. There is a significant risk of postoperative corneal exposure due to lagophthalmos and a poor Bell's phenomenon. Surgery is indicated only if ptosis interferes with vision or causes considerable social embarrassment. In these circumstances a small degree of ptosis correction often provides a marked improvement in the patient's quality of life. This paper presents a protocol for the management of ptosis in patients with CPEO and the results of its use in 17 patients.

The treatment protocol was based on the relative power of the affected muscles. Patients with good levator function were treated with an anterior approach levator advancement. The anterior approach was used to help the identification of structures, since the levator muscle and aponeurosis often show fatty infiltration. It also avoids interference with the conjunctiva and the tear film, which is often compromised in patients with CPEO.[2] Those with poor levator function but preserved frontalis action were treated by a brow suspension procedure. Lid props were prescribed when severe orbicularis weakness was demonstrable.

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CPEO may be considered as a gradually progressive external ophthalmoplegia which occurs in several disease states with numerous associated findings, hence Drachman's term, 'ophthalmoplegia plus'.[3] Some of the more common associations and other disorders which occasionally cause CPEO are listed in Table 1. Patients with myotonic dystrophy may give a history of autosomal dominant inheritance and have a classical long thin facies, frontal balding, and cataract.[4] Ptosis is marked, and there may be slowing or limitation of external ocular movements.[5] Kearns and Sayre[6] described a syndrome in which CPEO and heart block occurred before the age of 20 years, with diverse associated features and the later development of pigmentary retinopathy. Similar hereditary diseases include

Table 1 *Conditions associated with or causing CPEO*

Conditions Associated with CPEO
Myotonic dystrophy
Kearns Sayre syndrome
Stephens syndrome
Oculopharyngeal dystrophy
Disorders rarely causing external ophthalmoplegia
Congenital disorders
e.g. Abetalipoproteinaemia
  Refsum's disease
  Extraocular fibrosis syndrome
  Moebius syndrome
Progressive supranuclear palsy
Endocrine exophthalmos
Myasthenia gravis
Multiple sclerosis

Stephens syndrome[7] of CPEO, cerebellar ataxia and peripheral neuropathy, and oculopharyngeal dystrophy in which ptosis, mild restriction of eye movements, and dysphagia with autosomal dominant inheritance occur after 40 years of age.[8] Abetalipoproteinaemia[9] and Refsum's disease[10] are among rare congenital disorders which sometimes feature external ophthalmoplegia. Patients with ocular fibrosis syndrome have static restriction of ocular movement, with reduced movement of the globe on forced duction.

These syndromes must be differentiated from acquired brainstem disease, such as progressive supranuclear palsy, and from multiple sclerosis. Dysthyroid eye disease may rarely present in clinically euthyroid[11] ptotic patients, but the symptom of diplopia, uncommon in other forms of CPEO, together with particular restriction of elevation and abduction of the globe, may assist diagnosis. Myasthenia gravis is recognisable by the presence of muscle fatigue with a reduced number of acetylcholine receptors and a positive response to edrophonium, an anticholinesterase.[12] Weakness of the external ocular muscles is often asymmetrical and momentary retraction of the upper eyelid may be observed during refixations from down to straight ahead.[13] Surgical correction of myasthenic ptosis is influenced by the medical status of the patient and has an unpredictable outcome; patients with myasthenia gravis were therefore excluded from the study.

Table 2 *Patients treated for ptosis in CPEO*

Patient no.	*Age at onset of ptosis (yr)*	*Sex*	*Diagnosis*	*Surgery and age (yr)*	*Results*	*Follow-up (yr)*
1	10	F	Mit.M	R&L ALA 24	Abscess Lubric.	3
2	19	F	MD	R&L ALA 55	Good	2
3	33	M	OD	R&L ALA 46	Good	3
4	51	M	OD	R&L ALA 59	Good	3
5	41	F	CPEO	R ALA 61	Lubric.	1·5
6	43	F	MD	R&L ALA 51	Good	2
7	58	F	CPEO	R&L ALA 73	Good	3
8	7	F	CPEO	R&L SBS 62	Lubric.	0·5 1·5
9	11	M	KS	R&L ABS 41	Lubric.	1
10	11	F	KS	R&L ABS 15	Lubric.	7
11	12	M	KS	R&L ABS 20	Bands cut Ptotic+	5
12	16	M	KS	L SBS 49	Lubric.	1
13	24	M	CPEO	R&L ABS 59	Good	1
14	39	F	MD	R SBS 39	Good	2·5
15	64	F	MS	R&L SBS 78	Good	1·5
16	16	M	MD	spectacle-borne	Ptosis props	
17	51	M	CPEO	scleral lens		

Mit.M=Mitochondrial myopathy featuring CPEO. KS=Kearns-Sayre syndrome. MD=Myotonic dystrophy. MS=Multiple sclerosis. OD=Oculopharyngeal dystrophy. CPEO=Chronic progressive external ophthalmoplegia. ALA=Anterior levator advancement. SBS=Brow suspension using stored fascia. ABS=Brow suspension using autologous fascia. Lubric.= Lubricants required; good lid position.

Subjects and methods

Seventeen patients with severe ptosis and CPEO presented to the Lid Clinic at Moorfields Eye Hospital over a period of six years (Table 2). Patients with mild ptosis were not included in the study. Eleven patients had features of systemic disease: four had the Kearns-Sayre syndrome, two had oculopharyngeal dystrophy, four had myotonic dystrophy, and one had progressive multiple sclerosis. In all cases the diagnosis was confirmed by a neurologist. Specimens from triceps muscle biopsy in five patients, four of whom had Kearns-Sayre syndrome, had shown ragged red fibres, a marker for mitochondrial abnormalities.[14] At presentation a full clinical history was taken from each patient. Specific questions referred to the duration and variability of the ptosis, the use of props, diplopia, and the degree of disability suffered.

The palpebral aperture was measured with the patient looking straight ahead and levator function was measured from full downgaze to full upgaze with the frontalis muscle held fixed against the brow. The distance from the lid margin to the upper lid skin crease was noted when the latter was present. Bell's phenomenon and orbicularis and frontalis muscle function were assessed, and any evidence of corneal exposure was noted.

Surgery was performed to elevate the lids only if the ptosis occluded the visual axis or severely affected social function and some orbicularis function was present. If levator palpebrae superioris function was more than 4 mm, an anterior levator advancement, with aponeurotic resection or reinsertion, was performed under local anaesthetic,[15] the skin crease being set arbitrarily at 7 mm from the lid margin or being measured to match the other side. Patients with less than 4 mm of levator function and preserved frontalis action were treated by a brow suspension procedure.[16] If the patient was young, with good cardiac function, bilateral brow suspension procedures were performed under general anaesthetic by the Crawford technique[17 18] and autologous fascia lata. The anaesthetist was consulted at an early stage, and halothane, barbiturates, and suxamethonium were avoided.[19] In older patients, and where general anaesthesia was contraindicated, homologous fascia lata, stored in 70% alcohol and then soaked in saline for 12 hours and rinsed in soframycin 2% for 1 hour preoperatively, was inserted under local anaesthesia by the technique described by Fox.[20] Strips of stored fascia were cut 3 mm wide to ensure adequate strength, and the patients receiving them were given a five-day course of systemic antibiotic.

With both an anterior approach advancement and a brow suspension procedure the eyelid level was adjusted at surgery under local anaesthesia so that it was just clear of the pupillary axis with the patient voluntarily opening the eye. With a brow suspension under general anaesthesia the upper eyelid was positioned so that the lid was closed but just beginning to open at the end of the procedure. A 4/0 silk suture, inserted into the lower eyelid over a bolster and drawn up to the brow,[21] protected the cornea under the dressing. When the dressing was taken off 48 hours after surgery, the suture was taped to the cheek for 24 hours and removed at the end of this period if there was no evidence of corneal exposure; traction to the lower lid could be reapplied if this occurred. All patients were prescribed local antibiotic and lubricant drops on a 1/2 to 2 hourly basis.

All patients were reviewed at three or four monthly intervals in the clinic, with particular attention being paid to corneal exposure, and they were instructed to report immediately should the eye become painful, red, or start discharging pus.

Results

The series included four patients, three male and one female, with the Kearns-Sayre syndrome and an average age of onset of 12·5 years, and a fifth with mitochondrial myopathy without the complete syndrome; five with CPEO in isolation at the time of treatment, four of whom developed ptosis after the age of 20; two with oculopharyngeal dystrophy; four with myotonic dystrophy and an average age of 33·5 years at the onset of ptosis; and one with progressive multiple sclerosis. An anterior levator advancement was performed on seven patients (13 lids) with a mean levator function of 6·6 mm and a mean palpebral aperture of 4·4 mm. In no patient was preoperative levator function more than 8 mm. Two patients (four lids) responded to reinsertion of the aponeurosis and the remainder (nine lids) required an average resection of 9 mm. An example of the appearance of case 3 preoperatively and six months postoperatively is shown in Figs. 1a, b. In several cases histopathological study confirmed the fatty nature of the aponeurosis and levator muscle, and in one case mitochondrial inclusions were seen. Postoperatively there was little change in the mean levator function (7 mm), but the mean palpebral aperture increased to 7·6 mm. The mean follow-up was 30 months, ranging from 18 to 36 months.

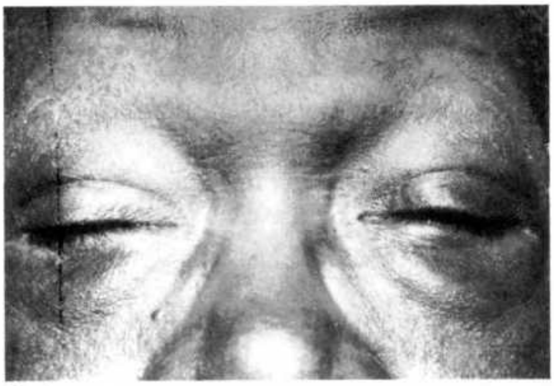

Fig. 1a

Fig. 1 *A 46-year-old man with oculopharyngeal dystrophy, a 13-year history of ptosis, and dysarthria for three years.* (a) *Preoperative.* (b) *Six months after bilateral anterior levator resection.*

Bilateral brow suspension with autologous fascia lata was performed on four patients with a mean age of 34 years, and stored fascia was used for another four patients (six lids) with a mean age of 62 years. The mean preoperative palpebral aperture was the same as for those patients with fair levator function, 4·4 mm, but mean levator function was only 3·6 mm. Postoperatively the mean palpebral aperture was 6·5 mm. The average follow-up was 30 months, ranging from 6 to 84 months.

Two patients with poor orbicularis muscle function were satisfactorily fitted with ptosis props.

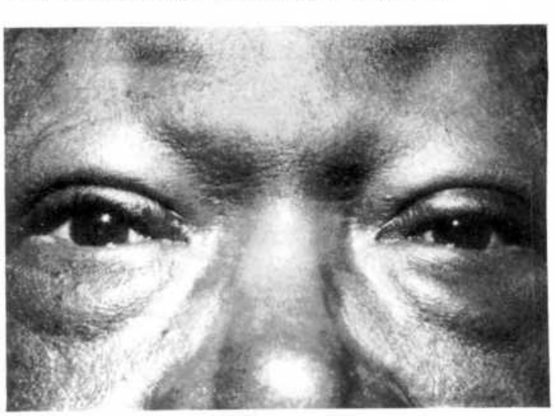

Fig. 1b

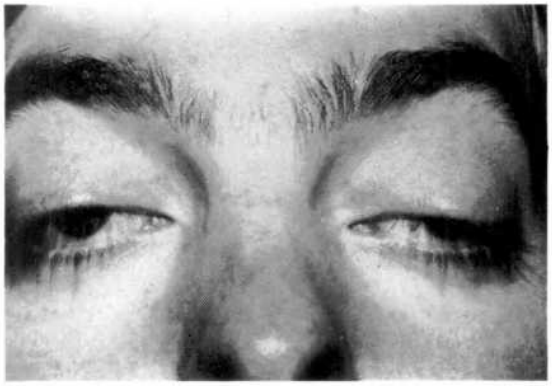

Fig. 2a

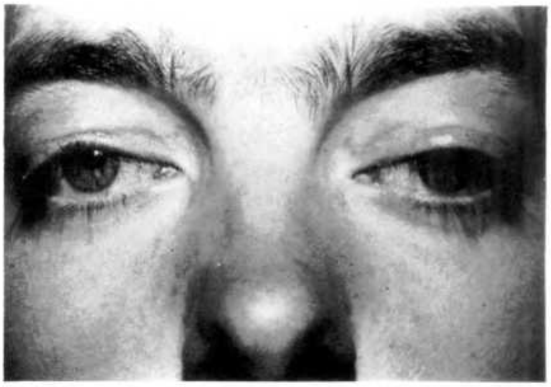

Fig. 2c

Fig. 2 *A boy of 15 years with the Kearns-Sayre syndrome and a two-year history of increasing ptosis.* (a) *Preoperative.* (b) *One year after bilateral brow suspension with autologous fascia lata.* (c) *Following resection of fascial bands.*

A 25-year-old woman developed a corneal abscess two months after a 10 mm right anterior levator resection. The palpebral aperture was only 7 mm but there was some lagophthalmos. The localised abscess resolved completely with appropriate medical therapy and there have been no further complications. Case 11, who had rapidly advancing ophthalmoplegic disease, developed marked corneal exposure within 12 months of a brow suspension procedure (Figs. 2a, b, c). The fascial bands on both lids were divided, and he has since developed recurrent occlusion of the visual axes. His facial muscles are now so weak that lid props are appropriate.

Discussion

Ptosis becomes a physical disability when the upper eyelid occludes the visual axis. The patient attempts to compensate by brow elevation and the adoption of an abnormal head posture with elevation of the chin. Surgery is often avoided for fear of corneal exposure problems. Ptosis props are usually not well tolerated by patients with early CPEO, but they are particularly useful when lid closure is very poor or the degree of ptosis is variable, as in myasthenia gravis. The long term use of scleral prop contact lenses may be associated with corneal pannus formation, though this has not occurred in the two cases described in this series. If the levator function is poor but frontalis action is good, we recommend a brow suspension. The patient must be warned that in either case the ptosis may recur if the levator or frontalis muscle becomes weaker. Alternatively corneal exposure may occur if the orbicularis muscle weakens and lid closure becomes defective. A lid lowering procedure may then be required, and eventually the patient may need ptosis props.

Corneal exposure did occur in this series after both levator resection and brow suspension, but bilateral upper lid lowering was required in only one case. Six patients, however, need lubrication in the form of hydroxymethylcellulose or 0·5% polyvinylpyrrolidine alkaline eye drops and with simple eye ointment at night, and two also tape their lids closed at night. These patients have shown marked reluctance to have upper lid lowering and would far rather persist with the insertion of drops and ointment than risk returning to their former ptotic state. The functional and cosmetic improvement following a brow suspension procedure in case 15 is shown in Figs. 3a, b. Some surgeons prefer the use of silicone to fascia for brow suspension, and its easy removal may facilitate lid lowering if required. As a foreign material it can easily become infected, and, although stored fascia can present similar problems, they are extremely rare in our experience and did not occur in this series. One patient, not included in this series, was treated with a blepharoplasty with a good result but marked lagophthalmos, requiring the frequent use of lubri-

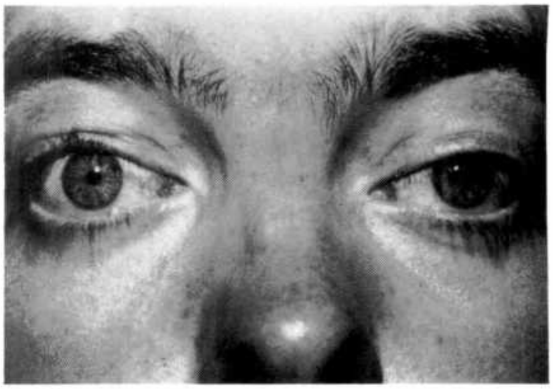

Fig. 2b

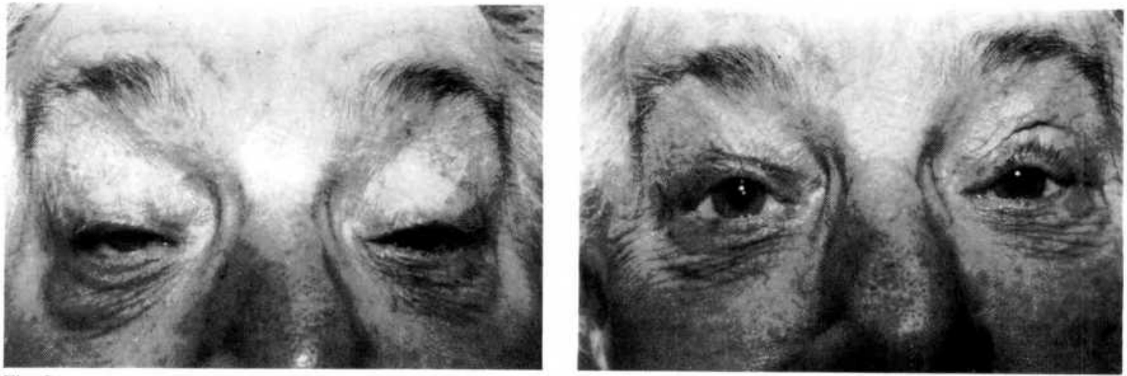

Fig. 3a

Fig. 3b

Fig. 3 *A 78-year-old woman with multiple sclerosis who underwent bilateral brow suspension with stored homologous fascia.* (a) *Preoperative.* (b) *Six months after surgery.*

cants. This procedure is not so easily reversed as those described here. Three patients with CPEO, treated for ptosis in other centres with a conventional degree of levator resection, have required surgical recession of the upper eyelid retractors because of corneal exposure.

In conclusion, we believe that if the orbicularis muscle function is very poor ptosis props are indicated, but if eyelid closure is fair patients are very much happier with surgical ptosis correction. Either a levator advancement or a brow suspension procedure should be performed, depending on the relative function of the levator and frontalis muscles. Corneal exposure problems may occur subsequently as the condition progresses and tear production decreases. It may be possible to improve corneal protection by raising and tightening the lower eyelid, but the surgeon must be prepared to lower the upper eyelid if the cornea cannot be preserved by this means or by using conservative measures. Patients must understand this before undergoing a ptosis correction. In this series all the patients who had ptosis surgery were most appreciative. They accept that more surgery may be necessary. The follow-up period is short, but we believe that this series justifies cautious surgery in the management of ptosis associated with CPEO.

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Ophthalmia neonatorum: study of a decade of experience at the Mount Sinai Hospital

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SUMMARY We reviewed the charts of neonates who received a diagnosis of conjunctivitis or ophthalmia neonatorum during a 10-year period at the Mount Sinai Hospital, New York City. Ninety-five cases were discovered, four of these were born elsewhere and were not subject to our protocol, which at present consists of intramuscular penicillin and topical tetracycline ointment (1%). The 91 cases represent an incidence of 3·1 cases per 1000 live births (9·1/year), an incidence approximately equal to that reported in other published studies. The clinical characteristics examined were: age, sex, race, birth weight, gestational age, Apgar scores, presence or absence of fever or other systemic illnesses, complications, type of delivery, time of year, incubation period, presence and type of discharge, uni- or bilaterality, Gram stain, Giemsa stain, culture results, antibiotic disc sensitivities, cervical culture, antibiotic therapy, sequelae, and type of prophylaxis received. Seven aetiological diagnostic categories were established: gonococcal (3%), chlamydial (3%), staphylococcal (30%), other pathogens (25%), chemical conjunctivitis (7%), culture negative/normal flora (22%), and unobtainable (10%). This distribution differs from others published. In contrast with other studies, moreover, we found few gonococcal and no chlamydial cases in neonates subject to the Mount Sinai Hospital treatment protocol. Correlation of clinical characteristics and aetiological categories showed no statistically significant trend. So far there have been no cases of ophthalmia neonatorum, treated as on our protocol, caused by penicillin resistant gonococci or chlamydiae.

Ophthalmia neonatorum, that is, conjunctivitis occurring within the first four weeks of life, has a notable history and was once a major cause of neonatal blindness. The syndrome has been associated with numerous organisms, which have varied in their relative importance over time.[1]

Clinicians are well aware that neonates very often develop a 'red eye' within the first few days of life. This is usually caused by trauma, chemical irritation, or transient infection. However, more serious forms of conjunctivitis do occur, and various methods of prophylaxis have been employed over the years to prevent the sequelae of the more serious pathogenic processes.

For over a hundred years Credé's instillation of silver nitrate solution has generally been the primary mode of prevention of gonococcal ophthalmia neonatorum. Silver nitrate, however, has many negative characteristics: (1) variable efficacy against modern strains of gonococci; (2) no efficacy against chlamydia (which may be the leading cause of ophthalmia neonatorum); (3) the possible induction of severe conjunctivitis by the solution itself; (4) blindness from accidental overdosing; and (5) the loss of efficacy from the postadministration saline wash.[2]

The Mount Sinai Hospital (MSH), New York City, introduced in 1952 the injection of 50000 units of aqueous penicillin intramuscularly (IM) to all liveborn infants in place of silver nitrate. So far we have had no immediate or short-term sensitivity problems with penicillin.[3] In 1982 a 1% tetracycline ointment instillation was added to this protocol.

The purpose of this retrospective study is to examine these prophylactic measures and the causes, incidence, clinical features, and treatment of ophthalmia neonatorum at MSH for the past 10 years.

Correspondence to Dr P A Asbell.

Materials and methods

The charts of all neonates (0–28 days) delivered at or presenting to MSH between June 1973 and June 1983 who received a diagnosis of conjunctivitis or ophthalmia neonatorum were reviewed. Clinical characteristics were recorded on a standardised clinical form and included: infant's age, sex, race, birth weight, gestational age, Apgar scores, presence or absence of fever, other systemic illnesses, complications and type of delivery, month of diagnosis, incubation period, presence and type of discharge, uni- or bilaterality, Gram stain, Giemsa stain, culture results, antibiotic disc sensitivities (where appropriate), cervical culture, antibiotic therapy, sequelae, and type of prophylaxis received.

The statistical analysis of data was by Pearson's χ^2 test and one-way analysis of variance. The analysis was performed on the actual numbers.

Results

Ninety-eight neonates received a diagnosis of ophthalmia neonatorum during the 10-year period. Three charts were unretrievable, and only 95 cases are presented here. Four of these were born elsewhere and were therefore subject to different prophylactic measures. During the study period a total of 30 345 live births were recorded at MSH. Undoubtedly some cases of ophthalmia neonatorum escaped detection because of the mild nature of the process and the possibility of neonates born here presenting elsewhere. Therefore this series represents a minimal incidence of 3·1 cases per 1000 live births, with an average of 9·5 cases per year, including those infants born elsewhere. Apart from those our series yields a similar incidence, with an average of 9·1 cases per year.

AETIOLOGY

Seven diagnostic categories were established by aetiology (see Table 1 for percentages and abbreviations).

The diagnosis of GON was made in three cases, representing 3·1% of all ophthalmia neonatorum cases in our study. The most recent was a case of a 2640 g boy born by an uncomplicated spontaneous vaginal delvery at MSH. He received 50 000 units of penicillin G intramuscularly at birth. He was a full-term neonate with Apgar scores of 7 (1 minute) and 8 (5 minutes) and had no systemic symptoms. A mild unilateral eye discharge developed on the third day of life, but a swab of conjunctival exudate sent to the microbiology laboratory in transport media grew only Staphylococcus epidermidis. Despite prolonged treatment with sulphisoxazole ophthalmic drops, scant mucus persisted in both eyes. He presented with ophthalmia neonatorum on day 19 of life.

Two months prior to the birth the father had visited Acapulco, Mexico. After his return to New York City the parents had sexual relations. The mother noted a new vaginal discharge one week before the delivery.

The infant was treated with penicillin G (100 000 units/kg/day) intravenously. Local therapy consisted of frequent saline lavage followed by topical penicillin drops (100 000 U/ml). The eyes improved markedly within 12 hours, although subsequent improvement was slower than expected. Culture of the conjunctiva grew *N. gonorrhoeae*. The organism produced a β-lactamase and was resistant to penicillin (MIC greater than 20 μg/ml). Cure was achieved with parenteral cephazolin (to which the isolate was sensitive) and topical gentamicin eyedrops.[4]

The second case was less certain but highly suggestive of GON. A full-term 2620 g girl was born vaginally with mid-forceps assistance due to slow progression of labour. Also of note during delivery was the premature rupture of the amniotic membrane more than 24 hours before birth. The neonate received 50 000 units of penicillin G prophylactically at birth but presented immediately with bilateral, purulent eye discharge and fever. Apgar scores were 8 at 1 minute and 10 at 5 minutes. The chart reviewed contained no record of Gram stain results, and eye cultures were negative. However, a gastric aspirate of the neonate was culture positive for *N. gonorrhoeae*, which was penicillin-sensitive. The mother had a history of partially treated gonorrhoea within six months of delivery. The infant was treated with penicillin G (100 000 U/kg/day) and gentamicin (6 mg/kg/day) intravenously. Both mother and child were discharged without complications. The follow-up examination was within normal limits.

The third case was one of a mixed infection described below.

Chlamydia can be demonstrated by one of three laboratory methods: (1) identification of typical

Table 1 *Aetiology of 95 cases of ophthalmia neonatorum**

Aetiology	*No.*	*%*
Gonococcal (GON)†	3	3·1
Chlamydial (ChON)†	3	3·1
Staphylococcal (SON)	29	30·2
Other pathogens (OON)	24	25·3
Chemical (CC)	7	7·4
Culture negative/normal flora (NON)	21	22·1
Unobtainable (UON)	9	9·4

*Includes four cases born elsewhere.

†Includes one mixed infection (gonococcal and chlamydial).

Table 2 *Results of conjunctival cultures in 24 cases of ophthalmia neonatorum due to other pathogens (OON)*

Culture results	*No. of cases*
Escherichia coli	9
Str. viridans	4
Str. fecalis	2
Str. pneumoniae	2
Staph. aureus and *E. coli*	2
Staph. aureus and *Pseudomonas aeruginosa*	1
Serratia	1
Klebsiella oxytoca	1
Enterococcus	1
Haemophilus parainfluenzae	1

Halberstadten-Prowazek inclusion bodies from conjunctival scrapings by means of iodine, Giemsa, or fluorescent antibody staining; (2) complement fixation or microtitre indirect immunofluorescence techniques; or (3) direct growth of the organism in embryonated hens' eggs or tissue culture systems.[5]

In this study, where conjunctival scrapings were obtained, prepared, examined, and noted in the charts by the house staff, method number one (1) above was employed as the diagnostic criterion for chlamydial ON (ChON).

Three cases of ChON were found, representing 3·1% of all cases of ophthalmia neonatorum in this series. Two of these had chart notations by house staff describing the inclusion bodies on Giemsa stain. The third case also had the bodies but was unique in that it was a mixed infection.

The mixed infection occurred in a 2920 g Hispanic boy who was the full-term product of a normal spontaneous vaginal delivery performed at another hospital where he had received silver nitrate prophylaxis. He presented to the MSH emergency room on the fourth day of life with a three-day history of a yellow, mucoid discharge from both eyes. Gram staining of scrapings revealed numerous polymorphonuclear leucocytes and Gram-negative diplococci morphologically typical of gonococci. Intravenous penicillin and eyedrops with saline irrigation were begun, with dramatic improvement. However, on day eight of life, while he was still receiving hospital treatment, bilateral conjunctivitis again developed. Gram staining now showed neutrophils and mononuclear cells but no bacteria and a repeat culture showed no growth. A Giemsa stain of conjunctival scrapings revealed epithelial cells with nuclear capping and intracytoplasmic inclusion bodies. The penicillin was stopped and the child was cured with sulphacetamide eyedrops.[6]

The next diagnostic category, staphylococcal ophthalmia neonatorum (SON), comprises those cases in which only *Staphylococcus aureus* was identified by standard bacteriological techniques, namely, growth on blood agar, coagulase positivity, and typical colonial morphology. The isolates were then subject to antibiotic disc sensitivity screening. *Staph. aureus* was the most frequent isolate in this study, found in 30·2% of all cases.

The category of 'other pathogens' (OON) consisted of 24 cases, representing 25·3% of all cases of ophthalmia neonatorum. Organisms isolated were subject to antibiotic disc sensitivity screening and are listed on Table 2.

Chemical conjunctivitis (CC) was diagnosed in seven cases (7·4%) and comprised those cases in which symptoms appeared within 36 hours of birth and in which smears, Gram stains, and cultures were negative or showed only a normal flora, that is, *Staph. epidermidis* and diphtheroids.

The culture negative/normal flora group (NON) represented those cases in which symptoms began after 36 hours, the Gram stain was unremarkable, and cultures were negative for growth or grew only normal flora. Twenty-one cases (22·1%) belonged to this category. Obviously there may be some overlap between the NON and CC groups as the two differed only temporally.

The records of the final group were either unobtainable or no record of cultures could be found in the chart or in culture report log books. Nine cases (9·4%) fell into this category (UON).

CLINICAL CHARACTERISTICS

The clinical data on our standardised chart review form were tabulated and compared for the aetiological categories. No statistically significant trend was demonstrated by χ^2 and, where appropriate, analysis of variance tests.

Of note is the fact that phototherapy treatment of the neonate did not produce any difference among the groups. Nor did premature rupture of membranes seem to predispose the infant to any of the established aetiological categories. However, for both the phototherapy exposed infants and for those who suffered premature rupture of membranes the absolute numbers were not sufficient to employ statistical analysis. In addition, according to the charts reviewed, no cervical cultures were performed and no sequelae were noted in any of the infants seen at follow-up.

Examination of monthly incidences revealed no monthly trends or seasonal variations when all seven categories were grouped. Also, if CC, NON, and UON categories are analysed as one group, again no trends or variations are evident. Hence, viral aetiology is unlikely.

The CC group showed no significant association with premature rupture of membranes, meconium

Table 3 *Ophthalmia neonatorum prophylaxis comparison at Mount Sinai Hospital**

	IM penicillin only	*IM penicillin and topical tetracycline*
Number of cases	85	6
Number of live births	25 845	4 500
Incidence cases per 100 live births	3·33	1·33
Number of cases by aetiology		
GON	2	0
ChON	0	0
SON	27	1
OON	22	2
UON	9	0
CC	5	2
NON	20	1

*Excludes four cases born elsewhere.

present at birth, type of delivery, or with tetracycline ointment instillation as prophylaxis.

Of interest is the fact that all ChON cases in our study were born elsewhere and thereby subject to other prophylaxis. No cases of ChON were reported at MSH under either of our protocols. Furthermore no cases of GON have occurred at MSH since IM penicillin and topical tetracycline have been given as prophylaxis.

As stated earlier, the type of prophylaxis employed at the MSH has recently changed. A comparison of the two protocols is outlined on Table 3. Although the number of live births during the two protocol periods differed by nearly a factor of six, the overall incidences when corrected for the number of cases per 1000 live births differed greatly. It is, however, too early to state conclusively whether this was due to the different protocols employed or to other factors.

Various types of treatment were applied in the cases of ophthalmia neonatorum examined in this series, ranging from normal saline irrigation alone to intravenous penicillin and topical antibiotic drops. The treatment given was dependent on the type and severity of infection diagnosed. Sulphafurazole eyedrops were the most often used treatment. They were also the primary treatment in SON and OON, the two most frequently occurring causes of ophthalmia neonatorum in our study.

Discussion

Greenberg and Vandow, in a review of ophthalmia neonatorum in New York City during the 1950s, found no cases of GON when IM penicillin was used as prophylaxis.[7] Furthermore IM penicillin has been found to be associated with a decreased incidence of early onset group B streptococcal disease.[3]

In more recent studies however, the changing picture of ophthalmia neonatorum has become apparent. The emergence of penicillinase-producing gonorrhoea (PPNG) and the increasing incidence of ChON show the need for implementation of better prophylaxis, diagnosis, and treatment.[1 6 8]

Chlamydia has been found in one study to cause nearly 50% of neonatal conjunctivitis.[9] Inclusion conjunctivitis, once considered benign and self-limited, has now been shown to cause micropannus, conjunctival scarring, and later recurrence, which can be prevented by local application of tetracycline before the twelfth day of life.[5] Both penicillin and silver nitrate are ineffective against chlamydia.

Because of the changing nature of the pathogens causing ophthalmia neonatorum MSH has recently updated its protocol.[10] We continue to give IM penicillin to prevent infection by the more prevalent penicillin-sensitive strains of *N. gonorrhoeae* and group B streptococcal disease. In addition since 1982 we have instilled 1% tetracycline ointment into the eyes of all newborn babies to eliminate the threat of PNGON and ChON.

Little controversy exists as to the benefit of prophylaxis in preventing ophthalmia neonatorum, especially GON. The debate has mainly centred on the choice of the agent which is the most effective and least toxic. Table 4 presents comparison studies based on both incidence of positive cultures and the occurrence of chemical conjunctivitis with different

Table 4 *Ophthalmia neonatorum: percentage (%) incidence with different prophylactic agents*

Investigator	*Silver nitrate*	*Other agents*
Jarvis *et al.**†	—	0·31 Overall
	—	0·33 IM penicillin
	—	0·13 IM penicillin and tetracycline
Stenson *et al.*†[8]	—	0·30 Overall
Armstrong *et al.*†[1]	0·19	0·38 Tetracycline
	0·86	—
Christian †[11]	1·3	0·68 Erythromycin
Jarvis *et al.**‡	—	0·07 Overall
	—	0·008 IM penicillin
	—	0 IM penicillin and tetracycline
Greenberg and Vandow‡[7]	0·03	0·36 Bacitracin
		0 IM penicillin
Posner *et al.*‡[12]	0·20	Bacitracin
Bickel‡[13]	0·15	0 Sulphacetamide
Franklin‡[14]	0·13	0 IM penicillin
Christian§[11]	8·7	3·4 Erythromycin
Franklin§[14]	6·0	2·1 IM penicillin
Harris§[16]	3·4	2·5 IM penicillin
Mathieu§[17]	46	6·0 Oxytetracycline
Wachter *et al.*§[18]	39	16 Erythromycin
Margileth§[19]	50	1·0 IM penicillin
		0·7 Bacitracin

*Excludes four cases born elsewhere. †All ON cases. ‡GON only §Chemical conjunctivitis only.

Table 5 *Ophthalmia neonatorum: comparison of incidence and aetiological breakdown*

	*Jarvis et al.**		*Stenson et al.*[8]		*Armstrong et al.*[1]
Incidence (cases per 1000 live births)	*Penicillin 3·33*	*Penicillin and tetracycline 1·33*	*Silver nitrate 1·9*	*Tetracycline 3·8*	*Silver nitrate 8·6*
Gonococcal (%)	2·3	0	2·3	4·7	14·2
Gonococcal and chlamydial (%)	0	0	N/A	N/A	1·0
Chlamydial (%)	0	0	33·0	31·0	28·5
Staphylococcal (%)	31·8	17·0	N/A	N/A	10·3
Chemical (%)*	5·9	33·0	N/A	N/A	1·6
Uncertain (NON and UON) (%)	34	17·0	30·0	27·0	44·4
Bacterial (%)	57·6	50·0	37·0	42·0	N/A

*Excludes four cases born elsewhere. †Definitions of chemical conjunctivitis differ slightly.

prophylactic agents. Stenson *et al.* found an overall percentage incidence of ophthalmia neonatorum of 0·30 cases, representing 3·0 cases per 1000 live births.[8] Armstrong *et al.* found an overall incidence of 8·6 cases per 1000 live births (0·86% incidence).[1] Christian found percentage incidences of 1·3 and 0·68 for silver nitrate and erythromycin prophylaxis respectively.[11] Our study found a percentage incidence similar to that reported by Stenson, namely, 0·31, representing 3·1 cases per 1000 live births. Under our earlier protocol of IM penicillin alone we found a 0·33% incidence, representing 3·3 cases per 1000 live births. Using the combined protocol of IM penicillin and topical tetracycline, we found a percentage incidence of 0·13, representing 1·3 cases per 1000 live births. These figures demonstrate a significantly small incidence while using both MSH prophylactic protocols.

Two studies of comparable design to ours are outlined in Table 5. As in our series Stenson *et al.*[8] compared two different prophylactic regimens and found 1·9 and 3·8 cases per 1000 live births for silver nitrate and tetracycline respectively. MSH protocols produced rates of 3·33 and 1·33 cases per 1000 live births for IM penicillin and IM penicillin with topical tetracycline respectively. Of all the studies cited, the MSH combined prophylaxis protocol resulted in the smallest ophthalmia neonatorum rate (1·33 cases per 1000 live births).

Our study also shows GON rates that are among the lowest of the studies cited in Table 4. In our 10-year series three cases of GON were found, in one of which the infant was born elsewhere. Hence two cases actually occurred under MSH protocol, while 30 345 live births were recorded here. This represents an overall incidence of 0·07 cases per 1000 live births (0·007% incidence) and 0·08 cases per 1000 live births (0·008% incidence) for IM penicillin alone, and no cases for IM penicillin combined with topical tetracycline. This is equalled by Greenberg *et al.*,[7] Posner *et al.*,[12] Bickel,[13] and Franklin[14] using the various forms of prophylaxis shown on Table 4.

The GON results summarised in Table 5 further reinforce the efficacy of the later MSH protocol as compared with others. All the ChON cases found in our series were born elsewhere. No cases occurred under either of the MSH protocols for the 10-year period. As discussed earlier, chlamydia can cause up to 50% of neonatal conjunctivitis.[9] Armstrong *et al.*[1] found chlamydia to be the prime cause of ophthalmia neonatorum in those cases where a cause was found. In their series it caused 28·5% of cases. Stenson *et al.*[8] also found chlamydia as the cause of ophthalmia neonatorum in a large percentage of cases, 33% and 31% for silver nitrate and tetracycline respectively. The disparity between these figures and ours is probably due to lack of experience at this institution with ChON. Only three cases have been diagnosed in the past 10 years.

An additional explanation for the disparity may be the fact that the importance of ChON has only recently been realised. Our study is retrospective, relying on notations in charts made up to 10 years ago. Often conjunctival scrapings were not performed, and when performed were not collected, stained and read properly. Moreover, the unknown group in our study is large, and may harbour undiagnosed ChON cases.

In our series the SON and OON groups represent a large percentage of all cases of ophthalmia neonatorum. SON accounted for 30·2% of the 95 diagnosed cases in this study, while Armstrong *et al.*[1] found staphylococcus to be the cause of only 10·3% of cases. Comparing our results with those of Stenson *et al.*,[8] who found about 40% (37 and 42) for all bacteria, we found that about 55% of cases at MSH to be bacterial in nature (see Tables 1 and 5). This is similar to Dumont and DeHaze's findings as well.[15]

The uncertain group (NON and UON in our study) showed percentages that were nearly equal for the three studies outlined in Table 5. In our series the uncertain cases represented 31·5% of all cases of ophthalmia neonatorum, which is somewhat disappointing.

The overall percentage incidence for the CC group in our study is 0·02 or 0·2 cases per 1000 live births, which is significantly smaller than the CC studies presented in Table 4. Although there is a large increase in CC in our study with the addition of topical tetracycline to our protocol, the incidence is only 0·4/1000 live births (0·04% incidence), which is again significantly less than that represented in the CC studies outlined in Table 4. However, Armstrong *et al.* found only 1·6% of ophthalmia neonatorum to be chemical in nature.[1] Their definition, however, was different from ours, namely, the appearance of symptoms within 24 hours with negative smears and cultures. Our category was defined to include the appearance of symptoms within 36 hours with normal flora.

Armstrong *et al.*[1] examined similar clinical characteristics in their study of 302 cases of ophthalmia neonatorum occurring at Grady Memorial Hospital from 1967 to 1973, and found certain clinical characteristics to be statistically significantly different, while our study did not. They found (1) a significant seasonal variation of GON and ChON; (2) that ChON occurred significantly more frequently in blacks than in whites; (3) that SON occurred more often in males (71%) than females but not significantly; and that the ChON incubation period of 8·1 days was significantly longer than the 6·5 day period for GON.

As stated earlier, our series revealed no statistically significant differences among the groups, including incubation periods. The type of discharge was characterised as purulent in 23% of cases in our series and 81% by Armstrong *et al.*[1] Fever was found in that study in only 9%, while we experienced it in 5% of cases. Armstrong *et al.*[1] also state that no uniform therapy for SON was found. In our series SON was treated with sulphafurazole eye drops in 45% of cases and OON treated as such in 58% of cases. Neither study reported ocular sequelae in its respective series.

CONCLUSIONS

Ophthalmia neonatorum remains an active clinical problem, probably with recent significant changes in its aetiology. Our series, however, is not consistent with this picture. In contrast with other studies, chlamydia did not prove to be a major cause of ophthalmia neonatorum at MSH. In addition a large percentage of cases (31·5%) in our series was without an aetiological diagnosis. These results emphasise the need for improved diagnostic efficiency. This may be accomplished by earlier referral before antibiotics are used and by the increased availability of culture and serological techniques to identify chlamydia.

The wide range of clinical characteristics investigated in our series did not reveal statistically significant differences between the aetiological categories. Of further benefit to the clinician would be a study examining whether these clinical characteristics are different for the entire ophthalmia neonatorum group as compared with normal neonates.

The decade of experience with ophthalmia neonatorum at the Mount Sinai Hospital has proved our prophylactic measures to be efficacious. The current protocol of IM penicillin and topical tetracycline thus far seems particularly advantageous, but further evaluation will be necessary to establish this conclusively.

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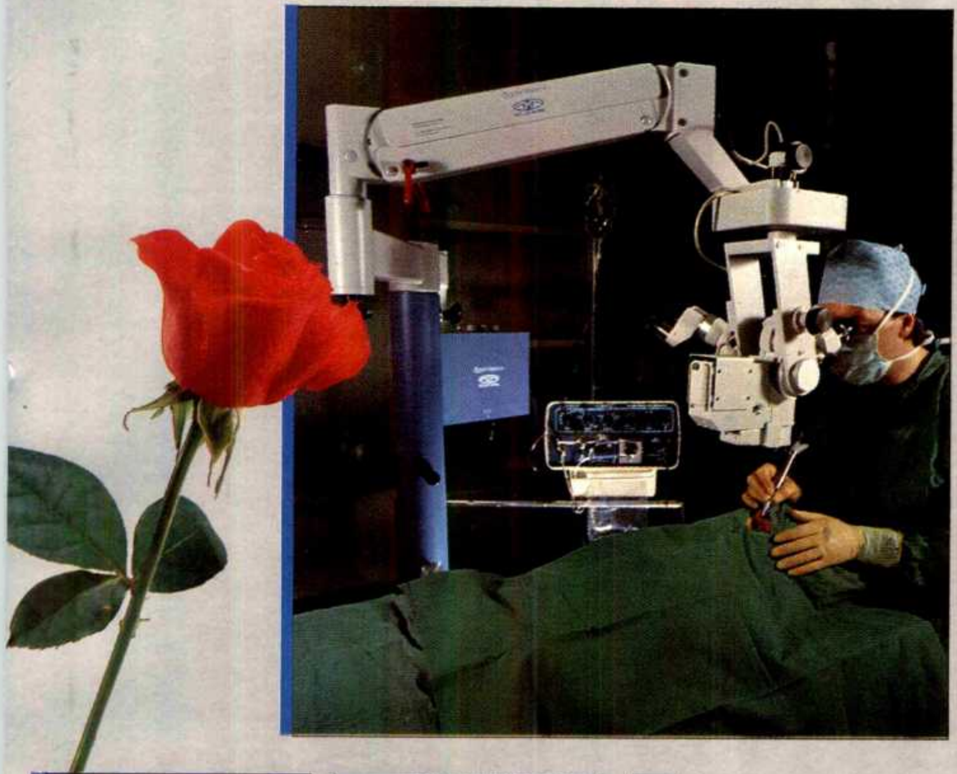

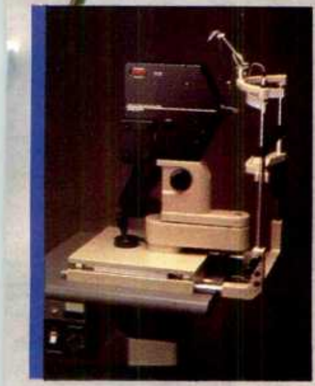

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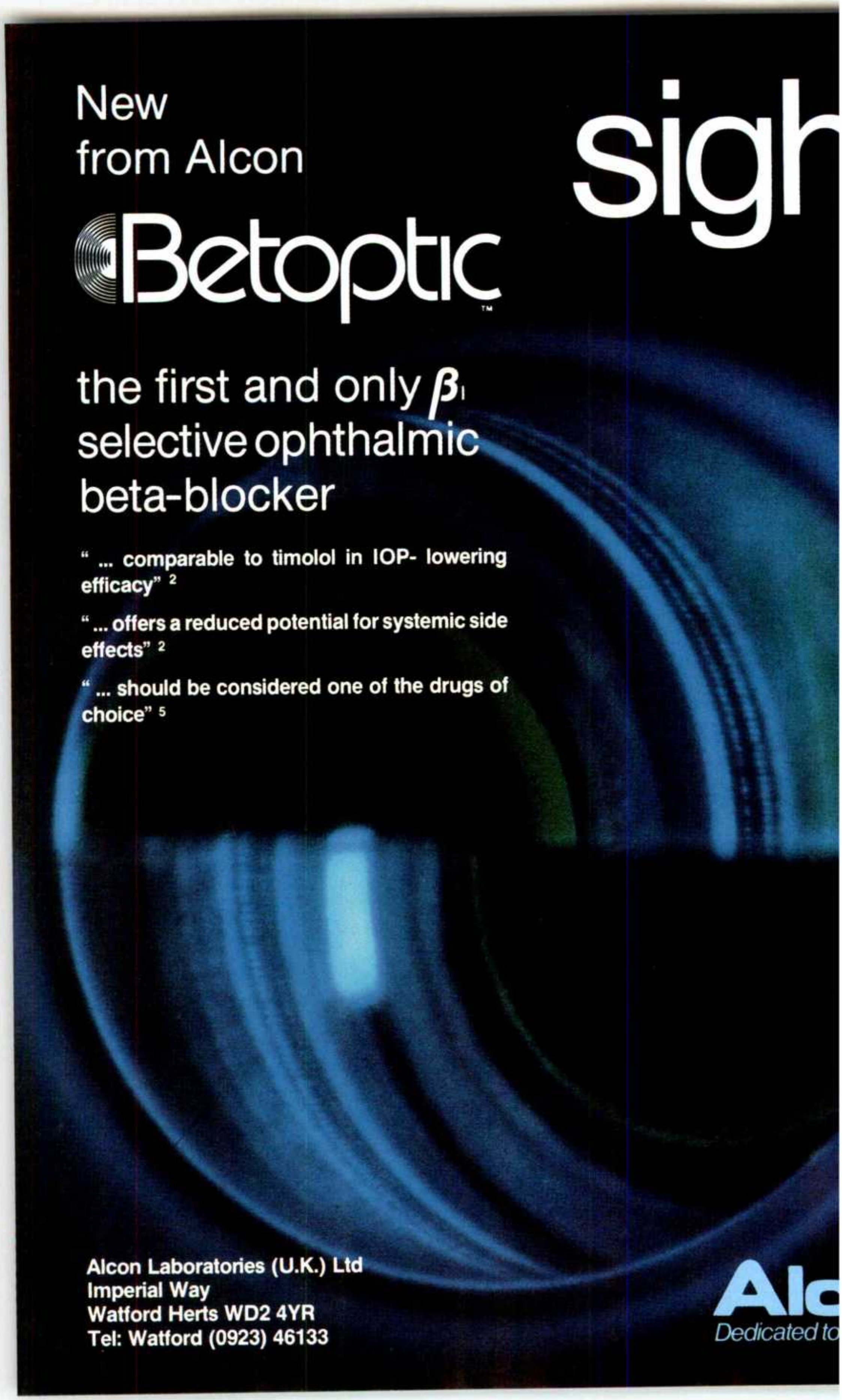

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Traumatic myopia; an ultrasonographic and clinical study

C A STEELE, A B TULLO, I B MARSH, AND J K STOREY

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SUMMARY Three patients with transient myopia following blunt injury are described with the aid of serial ultrasonography. The cause of refractive change is an increase in the anteroposterior thickness of the crystalline lens, which probably results from oedema of the ciliary body.

Myopia after concussional injury to the globe was first recognised by Kugel in 1870. Subsequent reports describing its transient nature, its association with hypotony, and the possible causes were reviewed by Duke-Elder.[1] We report three cases of marked but transient myopia following blunt ocular injury and show that ultrasonography is useful in its assessment.

Patients and methods

Ocular examination of all patients was performed on the Haag-Streit 900 slit-lamp utilising the Goldmann indirect gonioscopy lens and applanation tonometer. Refraction of all patients was by one of the authors (JKS). Measurements in Tables 1, 2, and 3 were derived by the use of the Stortz A scan biometric ruler. Fixation was on a distant point during measurement to control accommodation. In addition case three was examined by the Kretz A scan, Bronson-Turner B scan, and the combined A and B Ocuscan.

Case reports

CASE 1

A 14-year-old boy ran into the branch of a tree and injured his left eye. When he was first seen, four

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Table 1 *Serial measurements on injured and contralateral eyes*

Date	*Axial Length (mm)*		*A/C depth (mm)*		*Lens thickness (mm)*		*Vit. body (mm)*		*IOP*		*Refraction and visual acuity (injured eye)*
	R	*L**	*R*	*L*	*R*	*L*	*R*	*L*	*R*	*L*	
Day 3	23·9	23·3	4·0	2·6	3·5	4·0	16·4	16·7	ND	15	CF −6·25/+1·50×30° −6/9
Day 38	23·6	23·4	4·0	4·1	3·4	3·4	16·2	15·9	ND	14	6/5 −0·25 −6/5

*Injured eye.
Each figure given in Tables 1–3 is the average of at least five readings of the Stortz A Scan biometric ruler; mean readings given to one decimal point, but initial readings taken to two decimal points.
ND=not done. CF=counting fingers.

Table 2 *Serial measurements on injured and contralateral eyes*

Date	*Axial Length (mm)*		*A/C depth (mm)*		*Lens thickness (mm)*		*Vit. body (mm)*		*IOP*		*Refraction and visual acuity (injured eye)*
	R	*L**	*R*	*L*	*R*	*L*	*R*	*L*	*R*	*L*	
Day 3	24·7	24·2	3·9	3·4	3·4	4·0	17·4	16·8	15	8	CF −5·50/+0·50×170° −6/18
Day 17	24·6	24·5	4·0	4·0	3·3	3·4	17·3	17·0	ND	10	6/9 with pinhole −6/9
Day 38	24·8	24·8	4·0	4·0	3·4	3·4	17·4	17·3	ND	11	6/9−0·50 −6/6

*Injured eye.
See footnotes to Table 1.

Table 3 *Serial measurements on injured and contralateral eyes*

Date	*Axial Length (mm)*		*A/C depth (mm)*		*Lens thickness (mm)*		*Vit. body (mm)*		*IOP*		*Refraction and visual acuity (injured eye)*
	*R**	*L*	*R*	*L*	*R*	*L*	*R*	*L*	*R*	*L*	
Day 7	23·2	24·1	3·00	4·3	4·7	3·5	15·5	16·3	10	20	6/60 −5·50/+0·75×120° 6/24
Day 10	23·5	ND	4·1	ND	3·6	ND	15·9	ND	22	22	6/24 −2·00/+1·5×115° 6/9
Day 35	23·6	24·1	4·2	4·4	3·7	3·4	15·7	16·3	20	20	6/9 with pinhole −6/9

*Injured eye.
See footnotes to Table 1.

hours after the injury, the vision was reduced to hand movements in the left eye with correct projection of light. A total hyphaema was present, and the intraocular pressure was 24 mmHg. By day 3 most of the hyphaema had become absorbed and the intraocular pressure had fallen to 15 mmHg. The pupil reacted normally. The anterior chamber was now noted to be shallow, and the lens appeared thickened, with the iris bowed forward at 12 o'clock. Fundus examination at this stage required a myopic correction; a haemorrhage nasal to the disc was observed. Refraction revealed an emmetropic right eye, while the injured left eye improved from counting fingers to 6/9 with a correction of −6·25/+1·50 at 30°. Accommodation was fixed at approximately 20 cm. Two weeks after the injury the eye was still myopic, but at four weeks the myopia had resolved.

CASE 2

A 14-year-old boy was hit on the anterior inferotemporal sclera of the left eye by an airgun pellet fired from a pistol at a distance of approximately 30 feet (9 m). When he was first seen, 22 hours after the injury, the visual acuity was counting fingers with correct projection of light. A moderate hyphaema was present, and the intraocular pressure was 3 mmHg. The pupil was slightly eccentric and reacted sluggishly to light. Funduscopy on the following day revealed a normal disc, slight macular oedema, and an area of commotio retinae temporal to the posterior pole. A small amount of vitreous haemorrhage was present inferiorly. The visual acuity was 6/5 in the right eye but remained at counting fingers in the left. Refraction revealed an emmetropic right eye, while the injured left eye improved to 6/18 with a correction of −5·50/+0·50 at 170°. Accommodation appeared fixed at a distance of approximately 20 cm. Slit-lamp examination revealed a shallower anterior chamber on the left side and the appearance of a thickened lens. On day 3 gonioscopy of the left eye showed an open angle except for a small closed sector round the 3 o'clock meridian. Blood was present in the canal of Schlemm in the superotemporal quadrant. The intraocular pressure was 8 mmHg. Two weeks after the injury the pupils were equal and normally reactive to light.

CASE 3

A 23-year-old man was first seen 15 hours after being struck on the right side of the face by a football. He complained of blurred vision in the right eye. The visual acuity was 6/24, which improved to 6/9 with pinhole. Periocular bruising, a traumatic mydriasis, and cells and flare in the anterior chamber were observed. The intraocular pressure was 20 mmHg. Four days later the vision was 6/60 improving to 6/18 with a pinhole. Five days after the injury a hyphaema was present, the intraocular pressure had fallen to 12 mmHg, and the anterior chamber was first noted as being shallow. Ophthalmoscopy and retinoscopy confirmed the presence of myopia of −5·50/+0·75×120°, though an accommodative amplitude of 10 dioptres was recorded. Six days after the injury gonioscopy revealed angle recession in all quadrants and a cleft in the superotemporal quadrant, in which the iris was paretic. An ultrasonic B scan showed diffuse swelling of the uveal tract without detachment. Ten days after injury the anterior chamber deepened, the intraocular pressure rose, and the degree of myopia lessened. Funduscopy at this time revealed several choroidal tears in the superotemporal periphery and some macular oedema. Six weeks after injury the right eye was normotensive and had reverted to emmetropia, with a visual acuity of 6/9. Biometry, visual acuity, and intraocular pressure measurements of all three cases are shown in Tables 1–3.

Discussion

The three case reports clearly demonstrate that marked transient myopia can follow a variety of non-penetrating ocular injuries. The use of ultrasound to assess the intraocular dimensions allows a further evaluation of the possible explanations outlined by Duke-Elder[1] for this refractive change. No lens opacities were observed which might have caused an index myopia. Lengthening of the globe in these subjects was ruled out by ultrasonography, though such a change may occur as the result of blunt injury to the young eye many years later.[2] In all cases there was a large increase in anteroposterior thickness of the lens. As the vitreous cavity remained essentially unchanged in size, it was the forward movement of the anterior lens surface which resulted in shallowing of the anterior chamber. Myopia would result from (1) ciliary spasm, (2) ciliary body detachment, or (3) oedema of the ciliary body, all of which could result in an increase of lens size due to zonular slackening. Duke-Elder[1] considered that spasm of accommodation was probably responsible for the majority of cases of traumatic myopia and it could be reversed by cycloplegia. However, case 2 was treated with cyclopentolate from admission to hospital, and it did not prevent the development of myopia, suggesting that spasm was not the mechanism here.

Transient myopia is known to occur in the presence of uveal effusion. This association is a well documented clinical entity occurring in posterior scleritis,[3] after extensive photocoagulation,[4] and in Harada's syndrome.[5] It was postulated by Phelphs[6] in a case report of two subjects who developed angle closure as a result of forward displacement of the iris-lens diaphragm that the mechanism may be an anterolateral rotation of the ciliary body about its attachment to the scleral spur following the development of choroidal effusion. Our cases do not show a forward displacement of the iris lens diaphragm, but instead a marked anteroposterior thickening of the lens, suggesting that there has been no rotation of the ciliary body, but perhaps only ciliary body oedema. Transient myopia, in the absence of uveal effusion, follows the administration of some drugs.[7] In these hypersensitivity reactions ciliary body oedema is thought to be the mechanism.[8] Ciliary body oedema as a result of increased vascular permeability might occur as a direct result of trauma, perhaps caused by sympathetic paresis, since it has been demonstrated that most of the sympathetic nerve endings in the ciliary body terminate in the walls of blood vessels.[9]

The observation of transient hypotony in two of our cases supports the hypothesis that ciliary body function was compromised temporally. In case 3 B scan ultrasonography clearly demonstrated oedema of the whole uveal tract without detachment, and that is further evidence of ciliary body oedema as the cause of transient traumatic myopia.

We considered that the frequency of traumatic myopia may be underestimated and therefore undertook a small prospective study of 10 patients admitted for hyphaema. We found no significant changes in refraction or intraocular dimension. Thus traumatic myopia is probably not common. However, it is possible that cases are missed, because visual acuity measurement, especially on an injured child's eye, may be assumed to be inaccurate, and the presence of other signs, such as hyphaema, may be held responsible for diminished vision. The feature which should alert the observer to the possibility of traumatic myopia is shallowing of the anterior chamber in comparison with the uninjured eye.

We are grateful to Mr C L Dodd and Mr A E A Ridgway for permission to report on their patients. We also thank Mrs J L Noble and Dr E Rabie for performing and interpreting some of the ultrasonography. Patricia Quinn kindly typed the manuscript.

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A study of the haptic bearing angles in eyes with the Optiflex anterior chamber implant

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SUMMARY Gonioscopy and goniophotography were performed on 137 eyes with the Optiflex angle supported implant. At the time of gonioscopy the lenses had been in situ for a median of 20 months, with a range of 3–38 months. In 75·9% of cases one or both haptics were positioned posterior to the scleral spur with some degree of iris push. Iris tuck was seen in 29·2% of cases. Three different types of fibrous tissue formations were seen in the angles. The first two types (sleeving and iris haptic adhesions) occurred in the majority of cases and were haptic related. The third type was in the form of true peripheral anterior synechiae and occurred in 17·5% of cases. In cases with haptic related adhesions only, the angle remained open. Secondary glaucoma developed in 12 cases (8·7%). Ten cases had open angles. In the remaining two cases peripheral anterior synechiae were present in more than two-thirds of the angle, which was considered to be closed. Total burial of one of the haptics occurred in 25·5% of cases. A prominent iris vessel was observed near one of the haptics in nine cases. The thin looped haptics appear to stimulate fibrous tissue formation in the majority of cases. The haptic related adhesions add to the stability of the implant. It would make dislocation of the lens unlikely, even under severe trauma to the eye. However, once formed it would make removing the implant virtually impossible without severing the haptics. With time and with burial, the haptics seem to move away from the direction of the cornea. Total insulation of the haptic from the peripheral cornea is achieved with the occurrence of total burial.

Anterior chamber implants have been widely used as a primary procedure for the apparent ease of insertion. They are also used for secondary implantation in aphakic eyes. Gonioscopic studies have been performed on eyes with the Choyce mark VIII and Tennant lenses.[1 2]

The design changes of anterior chamber implants have been towards more flexibility and lighter weight. The flexibility in anterior chamber implants has been introduced to obviate the problems associated with sizing, postoperative tenderness, and astigmatism.[3] A number of different angle supported lenses have been developed with varying degrees of flexibility. Questions have arisen concerning the effect of such implants on the ocular structures, particularly so on the angle structures where the implant gains its support. If a lens implant has to be compressed to be inserted into the eye, the lens haptics store energy. Such energy must be released over a period of time.[4]

There has been a report on the early postoperative gonioscopic appearance of the anterior chamber (AC) implants with thin closed loop haptics.[5] This gonioscopic study reports the structural changes in angles that have been bearing such haptics for as long as three years.

Materials and methods

Over a period of four years the Optiflex AC implants were inserted into 515 eyes. The implant was inserted following intracapsular cataract extraction, either as a primary or as a secondary procedure. The Optiflex implant is a one piece lathe cut polymethylmethacrylate lens (Fig. 1). The lens has a 6 mm diameter optic and two closed looped haptics. The loops are thin and measure 0·24 mm in diameter.[6] An Optiflex implant (12 mm in length and of 19·5 dioptres) weighs 18 g in air. A weight of 20 g is required to produce a longitudinal flexion of the implant.[3]

Gonioscopy and goniophotography were performed postoperatively on 137 eyes of 130 patients.

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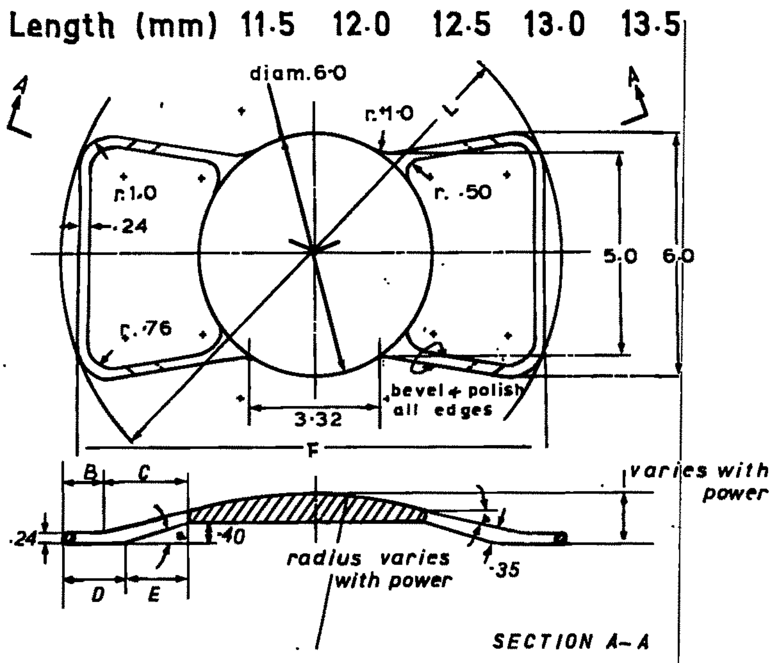

Fig. 1 *Dimensions of the Optiflex implant.*

Of the implants 134 were inserted as a primary procedure and three as a secondary procedure. Four eyes had unplanned extracapsular cataract extraction. Three eyes had operative hyphaema which was considered too minor to abort implantation. One hundred and thirty eyes had an uncomplicated intracapsular cataract extraction. Implants were inserted following the partial closure of the surgical wound and reformation of the AC. Air was used to reform the AC. Neither Sheet glides nor viscoelastic materials were used during the course of implantation. The size of the implant was estimated by measuring the corneal diameter and adding 0·5–1 mm. The implants used varied in diameter between 11·5 mm to 13·5 mm in 0·5 mm increments. The number of iridectomies varied from one to three according to the surgeon's preference.

Gonioscopy was performed from three months up to 38 months postoperatively. The Goldmann gonioscope together with the slit-lamp microscope were used to visualise the angle structures. A magnification of 25·6× was achieved with the objective power of 1·6× and (16×) oculars of the slit-lamp microscope. The Pentax ME super camera was mounted on the slit-lamp and used for goniophotography. A special adaptor incorporating one of the slit-lamp oculars was used. A 1000 ASA film was used for photography, and slit-lamp illumination provided the required lighting.

The position of each of the two haptics was noted in relation to the angle structures. The two haptics were classified as proximal and distal in relation to the incisional site. Each of the two haptics was judged to be in one of four positions:

(1) First position or position S. The haptic was situated against the scleral spur or between the scleral spur and the iris root without a significant iris push.

(2) Second position or position P. The haptic was situated posteriorly on the iris root with some degree of iris push but not tucked into an iris fold. The normally slit-like filtration angle has expanded in an anteroposterior configuration by the posterior bowing of the iris.

(3) Third position or position F. The haptic was tucked either partially or wholly into an iris fold.

(4) The fourth position, or position A. The haptic was situated anterior to the scleral spur.

Table 1 *The length of time implants have been in situ at the time of gonioscopy*

	Postoperative duration (months)	*Number of eyes*
Group 1	3–6	21
Group 2	7–12	39
Group 3	13–18	41
Group 4	19–24	15
Group 5	25–30	13
Group 6	31 and over	8
Total		137

Table 2 *Distribution of the lens length used among the 137 implants*

Implant length (in mm)	*Number of implants*	*Percentage*
11·50	11	8·0%
12·00	45	32·8%
12·50	57	41·6%
13·00	21	15·3%
13·50	3	2·2%

Changes in the peripheral iris were recorded. The presence of different types of fibrous tissue formations in the angle were described. Changes in the shape of the pupil were noted. Intraocular pressure was recorded in all cases prior to gonioscopy.

Results

At the time of gonioscopy the lenses had been in situ for a median of approximately 20 months with a range of three months to 38 months. Table 1 shows the length of time the implants had been in situ at the time of gonioscopy. The most commonly used size was 12·5 mm in length implant (41·6% of cases.)

Table 2 shows the distribution of the lens length used among the 137 implants.

In 30 eyes (21·9%) both haptics were in the position S. In 47 eyes (34·3%) one of the haptics was in position S and the other haptic was in position P. In all of the 47 eyes the haptic in the position P was the distal haptic. In 17 eyes (12·4%) the two haptics were in position P. In 40 eyes (29·2%) the distal haptic was tucked into an iris fold, position F. (Fig. 2). In this group the proximal haptic was in the S position in 16 eyes. In the remaining 24 eyes the proximal haptic was in position P. In three eyes the proximal haptic was found to be anterior to the scleral spur, position A. In this group the distal haptics were in position S. Table 3 shows the incidence of the different haptic positions in relation to the length of the implant used. Fig. 3 further illustrates the incidence of the posteriorly placed haptics in the different lens length groups. It would appear that in a total of 104 eyes (75·9%) at least one of the haptics was placed posteriorly. In all cases the posteriorly placed haptic either produced a change in the angle configuration or was tucked in an iris fold.

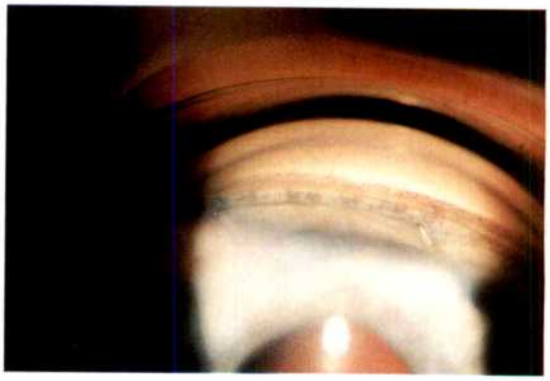

Fig. 2 *A goniophotograph showing one of the haptics tucked into an iris fold. (Gonio-view position).*

Delicate fibrous tissue coating one or both haptics was observed in 109 cases (79·6%). The fibrous tissue coating (or sleeving) was variable in extent. In most cases the sleeving was observed on the horizontal bar of the haptics (Figs. 4, 5). In a few cases it was also observed on the longitudinal limb of the haptic (Fig. 6). The incidence of sleeving did not change significantly with the length of time the implant was in situ (Table 4).

Coarse iris-haptic adhesions occurred in 83 cases (60·6%). Iris-haptic adhesions were pigmented and occurred predominantly at the corners of the haptics (Fig. 7). In most cases a combination of the sleeving and coarse adhesions was present.

Total burial of the horizontal bar of one of the haptics was observed in 35 cases (25·5%). In 33 cases the buried haptic was the distal haptic. Cases with a totally buried haptic included implants with haptics disappearing into an iris fold (Fig. 2). It also included cases where the horizontal bar of the haptic seemingly disappeared into a tunnel of fibrous tissue (Fig.

Table 3 *The different haptics positions in relation to the lens length*

Lens length in mm	*11·50*	*12·00*	*12·50*	*13·00*	*13·50*
Number of eyes	*11*	*45*	*57*	*21*	*3*
Number of cases in which one or both haptics were posteriorly placed (excluding cases with iris tuck)	5 (45·4%)	19 (42·2%)	29 (50·8%)	9 (42·8%)	2 (66·7%)
Number of cases in which one haptic was tucked into an iris fold	2 (18·2%)	12 (26·7%)	18 (31·6%)	7 (33·3%)	1 (33·3%)
Number of cases in which the two haptics were in the position S	4 (36·4%)	11 (24·4%)	10 (17·5%)	5 (23·8%)	—
Number of cases in which one of the haptics was placed anterior to the scleral spur	—	3 (6·7%)	—	—	—

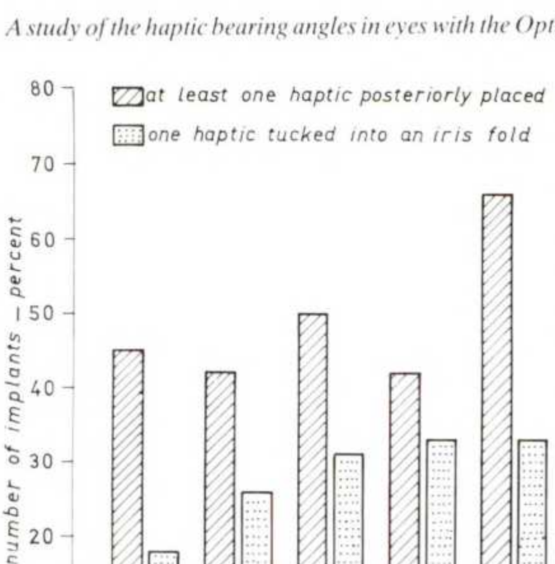

Fig. 3 *The incidence of posteriorly placed haptics in the different implant length groups.*

8). In the latter group the haptics in question were not necessarily posteriorly placed. The incidence of total burial increased significantly with the length of time the implant was inside the eye (Fig. 9). It had a peak incidence in the group which were examined by gonioscopy 25–30 months postoperatively. The incidence of total burial also increased with the length of the implant (Fig. 10). For implants longer than 12·5 mm the incidence was significantly high.

Sleeving and iris-haptic adhesions were confined to the implant loops. These two types of fibrous tissue formation did not appear to extend anterior to the scleral spur. They did not conceal the trabeculum in any of the cases.

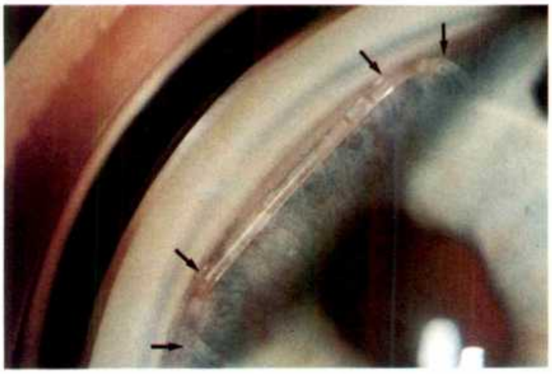

Fig. 4 *Goniophotograph showing sleeving at both ends of the horizontal bar (arrows). (Anatomical position).*

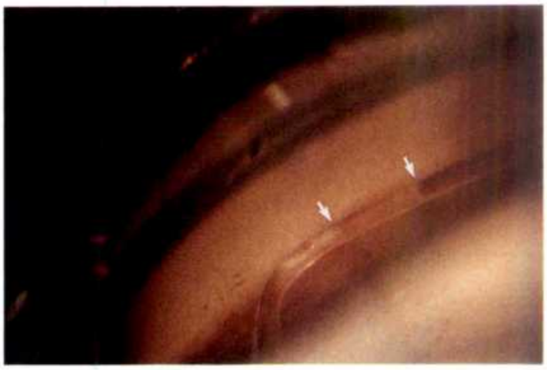

Fig. 5 *Goniophotograph showing sleeving along the horizontal bar (arrows). Note the slightly anterior position of the haptic. (Anatomical position).*

Peripheral anterior synechiae (PAS) were seen in 24 cases (17·5%). The height of the synechiae varied, but in all cases it extended from the iris and concealed the concavity of the angle recess. In 14 cases (10·2%) the PAS were limited to the superior part of the angle in relation to the surgical wound. In 10 cases (7·3%) the synechiae were observed in the four different quadrants of the angle. In all cases the distribution of the synechiae was not specifically related to the site of the haptics within the angle.

A prominent iris vessel was observed near the corners of the looped haptics in 9 cases (6·5%) (Fig. 8).

Among the 137 cases 12 had a persistent rise in intraocular pressure (8·7%). One patient had a trabeculectomy to control the intraocular pressure. Two patients had laser trabeculoplasties. They were controlled on medical treatment following the laser

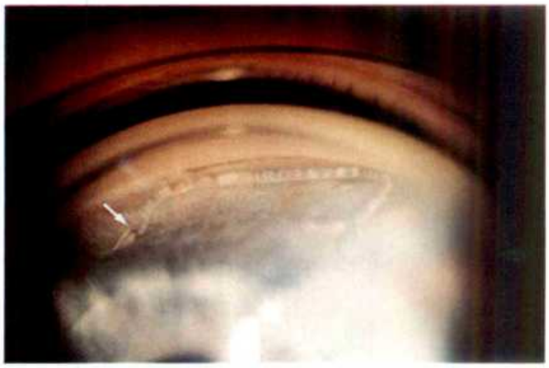

Fig. 6 *Goniophotograph showing sleeving of both the horizontal and vertical limbs of the haptic. Arrow marks the junction of the sleeved and non-sleeved parts of the vertical limb. (Gonio-view position).*

Table 4 *Incidence of fibrous tissue formation in the angle in relation to the postoperative duration*

Postoperative duration (months)	*3–6*	*7–12*	*13–18*	*19–24*	*25–30*	*31+*
Number of eyes	*21*	*39*	*41*	*15*	*13*	*8*
Number of eyes in which fine fibrous tissue coating of the haptics was evident	18 (85·7%)	32 (82·0%)	30 (73·2%)	13 (86·7%)	10 (76·9%)	6 (75%)
Number of eyes in which coarse iris-haptic adhesions were present	9 (42·8%)	24 (72·0%)	25 (60·9%)	10 (66·7%)	8 (61·5%)	7 (87·5%)
Number of eyes in which the horizontal bar of one of the haptics was totally buried	3 (14·3%)	6 (15·4%)	13 (31·7%)	5 (33·3%)	5 (38·5%)	3 (37·5%)

trabeculoplasties. In nine patients the intraocular pressure was controlled on medical treatment. In two cases more than two-thirds of the angle was found to be closed by peripheral anterior synechiae. In 10 cases the angle was considered to be open. Five cases had peripheral anterior synechiae extending for less than one-third of the angle. In the remaining five cases the angle was open all around.

The pupil was observed to be oval in 26 cases (18·9%). In all the 26 cases one of the haptics was grossly malpositioned and tucked into a large iris fold. Ovalling of the pupil was not observed in cases with minimal iris tuck. Table 5 shows the incidence of ovalling of the pupil in relation to the postoperative duration. From the table it is apparent that the incidence of ovalling of the pupil was not related to the length of time the implant had been in situ.

Discussion

Rigid angle supported implants were associated with sizing problems. Postoperative astigmatism, tenderness, iris tuck, and ovalling of the pupil are a few examples. Uveitis—glaucoma—hyphaema, or the so-called Ellingson syndrome, was described with the early angle supported AC lens implants.[7] The syndrome represented the result of interaction between the implant and the ocular structures in the angle.

A generation of highly flexible and semiflexible implants were introduced to minimise the complications seen with the early rigid AC lenses. The basic changes in the design of the implant were towards a lighter weight and higher flexibility. The changes were also aimed at minimising the contact between the implant and uveal tissues by improving the lens vault.[8]

Within the angle it would appear that the ideal site for the implant haptics to fixate is against the relatively inert scleral spur. In this study only 21·9% of the implants had both haptics at the level of the scleral spur. In the majority of cases (75·9%) the position of one or two of the haptics was found to be posterior to the spur. Histopathological studies of eyes with semiflexible and closed loop implants have shown most of the haptics to be posterior to the scleral spur, with a variable degree of uveal tissue penetration.[9,10] The incidence of posteriorly placed haptics did not vary significantly with the length of the implant used. Iris tuck was present in 29·2% of cases. With the exception of the size 11·50 mm the incidence of iris tuck has not increased significantly with the length of the implant. The incidence in the 11·50 mm group was lower at 18·2%. It would appear that iris tuck is an inherent complication of insertion of this type of lens.

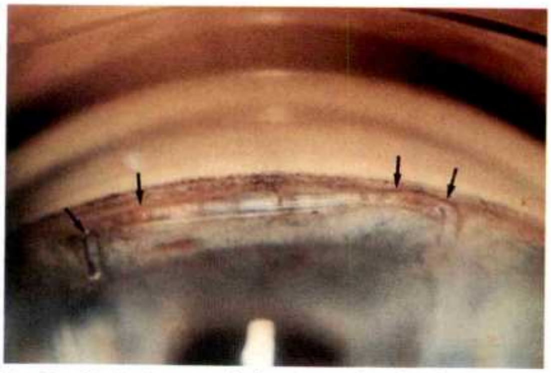

Fig. 7 *Goniophotograph showing two bands of coarse iris haptic adhesions at both corners of the haptic (arrows). (Gonio-view position).*

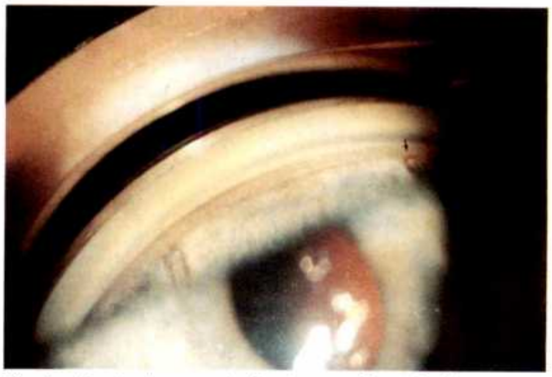

Fig. 8 *Goniophotograph showing total burial of the horizontal bar of the haptic into a tunnel of fibrous tissue. Note the presence of a prominent iris vessel (arrow) near one of the corners of the haptic. (Anatomical position).*

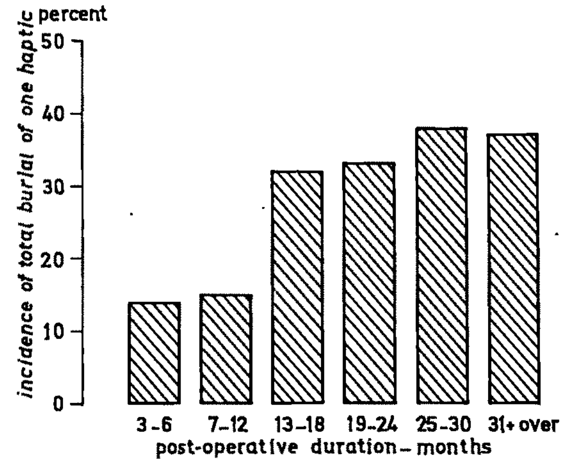

Fig. 9 *The incidence of total burial of one haptic in relation to postoperative duration.*

It is of interest to know that Kraff *et al.*[1] reported an incidence of 28% of iris tuck with the rigid Choyce's and Tennant's implants. The Optiflex implant is not as flexible as other lens implants in the semiflexible range. A weight of 20 g is required to flex the Optiflex implant as compared with a 7 g for the semiflexible Leiske's lens. On the other hand the implant is not as rigid as the Choyce mark IX, for instance, where a weight of 208 g is required to produce flexion.[3] Perhaps the Optiflex implant would be best described as a semirigid lens.

Three distinctly different types of fibrous tissue formations were seen in the angles supporting the Optiflex implant. A combination of two or more of these were seen in the same angle. The first type was in the form of delicate fibrous tissue coating the thin loops and best described as sleeving. It occurred in 79·6% of cases. The extent of sleeving varied, and in the majority of cases it involved the horizontal bar mainly. The second type was in the form of coarse iris haptic adhesions. It occurred predominantly at the junctions between the horizontal bar and the vertical limbs of the loops. This type of adhesion was more pigmented than the first type, and it was seen in 60·6% of cases. The aetiology of sleeving and iris haptic adhesions remains speculative. Mechanical activation of the iris stromal fibroblasts by lens haptics has been postulated as a possible mechanism.

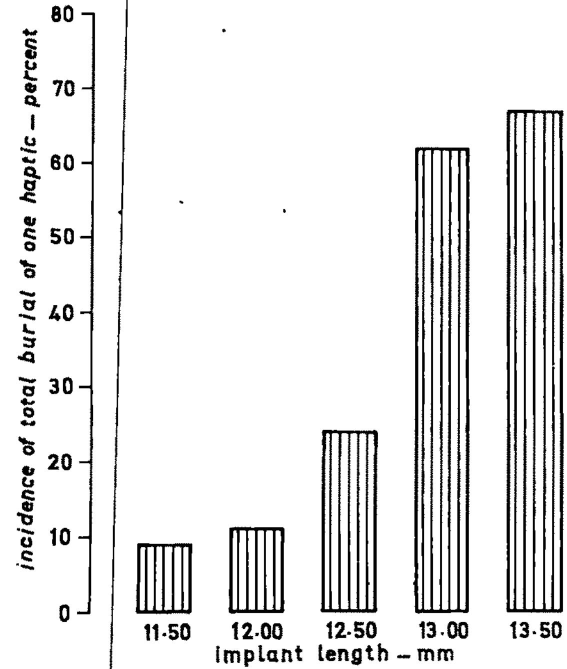

Fig. 10 *The incidence of total burial of one haptic in the different implant length groups.*

This was histologically proved with some of the polymethylmethocrylate (PMMA) implants.[11] Inflammatory changes in the angle are another possible mechanism.[5]

The site of the coarse iris haptic adhesions at the point of maximum iris contact (the corners of the haptics) suggests mechanical stimulation as a possible mechanism. The fact that sleeving has been seen on haptics which were not in direct contact with the iris suggests inflammation as a possible mechanism. However, a combination of mechanical stimulation and inflammation probably exists in all cases.

Total burial of the horizontal bar of one of the haptics occurred in 25·5% of cases. Total burial is probably the result of direct pressure on the iris and ciliary body together with mechanical stimulation of these tissues. It is also possible that inflammation has a minor role. The involvement of the distal loop in nearly all cases of burial is significant. The induction of haptic burial, mostly inferiorly, was reported by

Table 5 *Incidence of ovalling of the pupil in relation to the postoperative duration*

Postoperative duration (months) *Number of eyes*	*3–6* *21*	*7–12* *39*	*13–18* *41*	*19–24* *15*	*25–30* *13*	*31+* *8*
Number of eyes with oval pupil	4 (19·0%)	8 (20·5%)	6 (14·6%)	4 (26·6%)	2 (15·4%)	2 (20·0%)

Poleski and Willis[5] with two different semiflexible implants. The weight of the implant is insignificant. This is because the specific gravity of the PMMA (1·19) is similar to the specific gravity of the aqueous (1·01).[3] The predominant burial of the distal loops could be more readily explained by their position. They are more likely to be placed posteriorly on the iris.

The first two types of fibrous tissue formations were confined to the implant loops. In almost all cases they have not extended anterior to the scleral spur. They have not concealed the trabecular meshwork, and the angle remained open. The first two types do not constitute true peripheral anterior synechiae. They represent the interaction between the haptics and ocular structures. The third type was in the form of peripheral anterior synechiae which concealed the concavity of the angle recess. The incidence of PAS in the superior part of the angle (10·2%) is lower than the reported incidence of 35% following uncomplicated cataract extraction.[12] The distribution of PAS within the angle makes it highly unlikely that the loops played any part in its formation. Transient pupil block and angle closure is a possible mechanism in the formation of PAS in the different parts of the angle. Rowsey[12 13] and Gayler *et al.* have suggested that the presence of an intraocular lens at the site of PAS would lead to gradual tilting of the implant. The postulated direction for the tilt of the implant was forward and superiorly. This is perhaps true when an implant haptic is placed in contact with a previously formed PAS. In this series, with the formation of the haptic related fibrous tissues the direction of shift (if any) seems to be away from the cornea.

The significance of the presence of a prominent iris vessel near one of the haptics is not clear. It appeared in 6·5% of cases, none of which had any neovascular changes in the rest of the angle. The constant site of the vessel, near the point of maximum pressure of the haptics (the corners), suggests localised iris stromal atrophy as a possible mechanism. The vessels are probably normal iris vessels which became apparent as a result of the stromal atrophy. The incidence of 6·5% is significantly lower than the 30% figure reported with the more rigid angle supported implants.[1] This is not surprising, as we know that the Optiflex implant has a linear compressibility of 20 g compared with 208 g for the more rigid implants.[3]

Secondary glaucoma developed in 12 cases (8·7%). In two cases the mechanism of glaucoma was clearly that of a closed angle. In 10 eyes the angles were open and functional damage to the trabecular meshwork must exist. Trauma, inflammation, and inflammatory products would all be contributory factors. The general incidence of pseudophakic secondary glaucoma was estimated by Layden to be 8%.[14]

Ovalling of the pupil, representing gross iris tuck, was present in 18·9% of cases. Pearce's study of the more rigid Choyce lenses showed that 25% of cases had peaked pupils.[15]

CONCLUSION

The Optiflex implant still retains some of the characteristics of the rigid angle supported implants. There is a tendency for the implant haptics to be placed posterior to the scleral spur. Sizing of the implant is important, though not as critical as in the more rigid lenses. The thin looped haptics stimulate fibrous tissue formation. In the majority of cases, with haptic related adhesions only, the angle remained open. Fibrous tissue formation around the haptic adds to the stability of the implant. It would make dislocation of the lens unlikely even under severe trauma to the eyes. However, once formed it would make removing the implant virtually impossible without severing the haptics. With time and with burial the haptics seem to move away from the direction of the cornea. Total insulation from the cornea is achieved with the occurrence of total burial.

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Congenital deficiency of meibomian glands

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SUMMARY A 16-year-old girl presented with contact lens intolerance. She was found to have a marked deficiency of meibomian glands in the upper lids and almost total absence in the lower lids. Evidence of tear film instability was found and attributed to deficient lid oil production. A daily wear soft contact lens was later fitted and tolerated.

Meibomian lipid forms the anterior layer of the tear film.[1] It is believed to retard evaporation from the preocular tear film and to prevent contamination of the tear film by the more polar skin sebum of the cutaneous surface of the lid margin.

Meibomian lipid is secreted by the meibomian glands, which are radially disposed and serially arranged within the substance of the tarsal plate, with their ductular openings placed on the cutaneous side of the mucocutaneous junction. This ideal placement permits the delivery of meibomian oil on to the anterior aspect of the tear film, where it spreads over the aqueous film as the eyes open after each blink.

Histologically the glands are racemose holocrine glands, whose acini open into a central ductule lying at right angles to the lid margin. The acini form a series of yellowish grape-like clusters, distributed at intervals along the length of the central ductule and clearly visible through the conjunctiva of the tarsal plate in young adults. With increasing age these acinar details are less visible, though a yellow streak can be seen representing each gland. The glands are also visible by transillumination through the lid,[2-5] and an interesting infrared technique (meiboscopy) has been developed.

The ductular orifices at the lid margin are visibly surrounded by a cuff of epithelial tissue, which has a delicate vasculature visible by fluorescein angiography.[3] The orifices are flush with the surface in health and arranged, usually in a single line, parallel but anterior to the mucocutaneous junction. At times the line is less regular and may give the impression of a duplication in the antero-posterior direction. The epithelial cuff is of similar pink colour to neighbouring lid margin tissue. In black people the orifices are outlined by pigment, and are more readily seen.

There are more glands in the upper than the lower lid (30–40 in the upper and 20–30 in the lower). Gentle pressure through the lid on to the globe impresses the tarsal glands and expresses a clear fluid lipid on to the lid margin. Meibomian oil is liquid at lid temperature (with an upper melting point range at 32·0–33·8°C).[6] The stimulus for secretion of meibomian lipid is not known.

Although disease of the meibomian glands is common as part of meibomitis, in association with marginal blepharitis, or with chalazia, or rosacea, there are few reports relating such abnormality to surface ocular disease. However, various authors[7-10] referred to conjunctivitis accompanying meibomian gland disease, and Bron and Tripathi (1973) to a specific form of epithelial keratopathy caused by meibomianitis (cystic epithelial keratopathy).[11] Thygeson[12] considered the role of staphylococcal toxins in blepharoconjunctivitis. Epithelial keratitis has been described by McCulley and Sciallis associated with meibomianitis.[13] It has been assumed that such manifestations are due to a deficiency of the normal conservative function of the meibomian lipid in retarding evaporation, and represent an induced non-wetting eye disease.

An alternative explanation relates to bacterial infections of the meibomian glands and to suggested toxic meibomian lipid degradation products.[13 14] The action of fatty acids released by bacterial lipases is a related hypothesis.[15]

Case report

The present paper reports absence of meibomian glands in a young contact lens wearer. In September 1981 a 16-year-old white American girl (OEH 196501) was referred to the Oxford Eye Hospital

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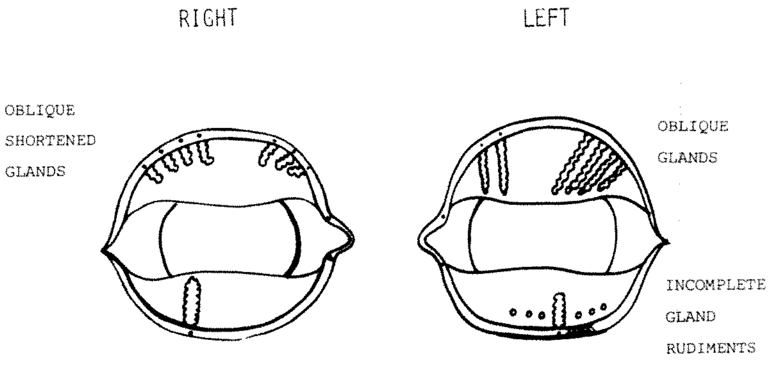

Fig. 1 *Diagram to illustrate the disposition of residual meibomian glands.*

from an American Air Base with a history of one and a half months of soft contact lens wear using cold chemical sterilisation. She reported increasing redness of the eyes, and in the two weeks before presentation she developed marked pain in both eyes. She stopped lens wear for one week and was started on chloromycetin solution qds without relief. A marked 'corneal stipple', with punctate staining in the left more than the right eye, failed to resolve over this period. Acuity was reduced in each eye.

Acuity in the casualty department was RE 6/9 and LE 6/12 corrected, improving to RE 6/5 and LE 6/6+3 with a pinhole. There was bilateral punctate keratopathy. Examination in the external disease clinic two days later showed bilateral upper tarsal conjunctival papillae of mild degree and a few follicles and cystic changes below. There was a 2+ interpalpebral conjunctival and corneal punctate epithelial staining. Anterior segments and fundi were otherwise normal.

At the next visit it was recognised that there was a major abnormality of the meibomian glands which were noted to be both deficient in number and abnormal in morphology (Fig. 1). The right upper lid had 14 orifices associated with obliquely disposed glands about a quarter their normal length. They were absent from the central part of the lid. In this region there was the occasional suggestion of a gland which failed to come in contact with the surface of the lid margin. The right lower lid showed a single gland and orifice. On the left the upper lid had 16 orifices. Glands were elongated and obliquely disposed in the temporal part of the tarsal plate, and more vertically disposed in the nasal part of the lid. Many were approximately of normal length. The left lower lid had a single short gland about half the normal length. On either side of this solitary gland was a line of dark, rounded spots in the line of the subtarsal fold, which were assumed to be abortive tarsal gland rudiments. There was no connection with the lid margin. Just temporal to the solitary gland orifice was a patch of presumed squamous metaplasia across the breadth of the lid margin.

Otherwise the lid margins were normal in appearance, and, where meibomian orifices were visible, they were disposed at their normal location in the mucocutaneous junction; slight pouting was present in some. Oil was expressible from the upper lid gland orifices on the right. No oil was expressible from the other lids. Over the period December 1980 to 1981 the fluorescein breakup time (BUT) was measured on a number of occasions: R 4–8 s, L 6–8 s; R 15 s, L 5 s; R 9 s, L 7 s; R 5 s, L 6 s. Schirmer's test was R 15 and 12 mm in 5 minutes, and L 10 and 5 mm on separate occasions.

The patient was a myope. Refraction was R −2·75/+0·5 axis 25°=6/4 and L −2·75/+0·50 axis 170°=6/4. K readings were R 7·5 along 90°; 7·35 along 150° and L 7·5 along 110°; 7·40 along 30°. About one year after presentation she was refitted with a Scan soft lens and achieved all day wear (7·00 am–9·00 pm in February 1982). There was a tendency to stinging in the left eye during wear, after prolonged staring. There was a tendency to accumulate deposits on the right lens, which necessitated changing the wearing schedule.

Discussion

The present study reports a patient with meibomian glands which are deficient in number, rudimentary in form, and abnormally disposed. The absence of any but minor conjunctival signs (interpalpebral staining and upper tarsal papillae) and the youth of the patient strongly suggest that this is a congenital abnormality of the glands. The patient was otherwise normal, and there was no skin complaint. There are few reports of congenital absence of meibomian glands. Holly and Lemp refer to an association with anhydrotic ectodermal dysplasia.[16]

One of us (AJB) has seen a similar case, also female, in another institution. In this patient symptoms were present from infancy.

Symptoms in our patient are assumed to be due to a deficiency of meibomian oil. Meibomian oil is thought to prevent evaporation from the ocular surface. In the rabbit Mishima and Maurice estimated that meibomian oil reduced evaporation by 4–20 fold.[17,18] Brown and Dervichian[19] could not confirm this conservational effect of meibomian oil on water loss. But, although human meibomian oil has a different composition from rabbit meibomian oil,[20,21] it is difficult to accept that it does not perform this function, since it forms a multimolecular sheet across the preocular surface between blinks in normal subjects. The other postulated function of meibomian oil is to prevent contamination of the ocular surface with sebaceous lipid present on the lid skin[22] and derived from lash-associated sebaceous glands. The ability of sebum to lower the surface tension of preocular tear meibomian lipid has been graphically demonstrated by McDonald, who showed that a sebum covered hair touched on to the preocular surface causes an immediate disruption of the lipid film.[23] The presence of hydrocarbons in meibomian oil collected by expression from normal lids[21,24] suggests that some contamination of the meibomian secretion may occur normally. Norn has shown that lipid on the lid margin can find its way into the conjunctival sac and draws the same conclusion.[25]

A deficiency of normal lid oil in the tear film and perhaps the presence of sebum on the tear film would be expected to encourage evaporation from the ocular surface and symptoms and signs of non-wetting. The interpalpebral staining pattern and reduced BUT recorded in our patient are in keeping with this. In the study by Bron and Tripathi, a particular form of epithelial surface change was observed and termed cystic epithelial keratopathy, associated with the meibomian blockade and other features of meibomianitis.[11] In that situation epithelial cysts are observed in the exposed region of the cornea, together with punctate erosions and punctate epithelial keratopathy.

In our patient symptoms appeared after institution of contact lens wear, despite the likelihood that the oil gland deficiency was congenital. This suggested that contact lens wear precipitated the surface changes. Punctate interpalpebral staining gradually decreased once contact lens wear had been stopped but did not entirely disappear. Punctate corneal changes may be slow to subside after contact lens problems whatever their cause; therefore it is not certain that their persistence was due to the poor wetting or to contact lens 'insult'. It is our impression that clinical presentation of non-wetting problems due to aqueous deficiency or meibomianitis of congenital or early onset does not necessarily occur in infancy but may start to produce symptoms in the teens or twenties. This suggests that the ocular surface may be more resilient in the young. A change in lens and regimen ultimately permitted contact lens wear in this patient.

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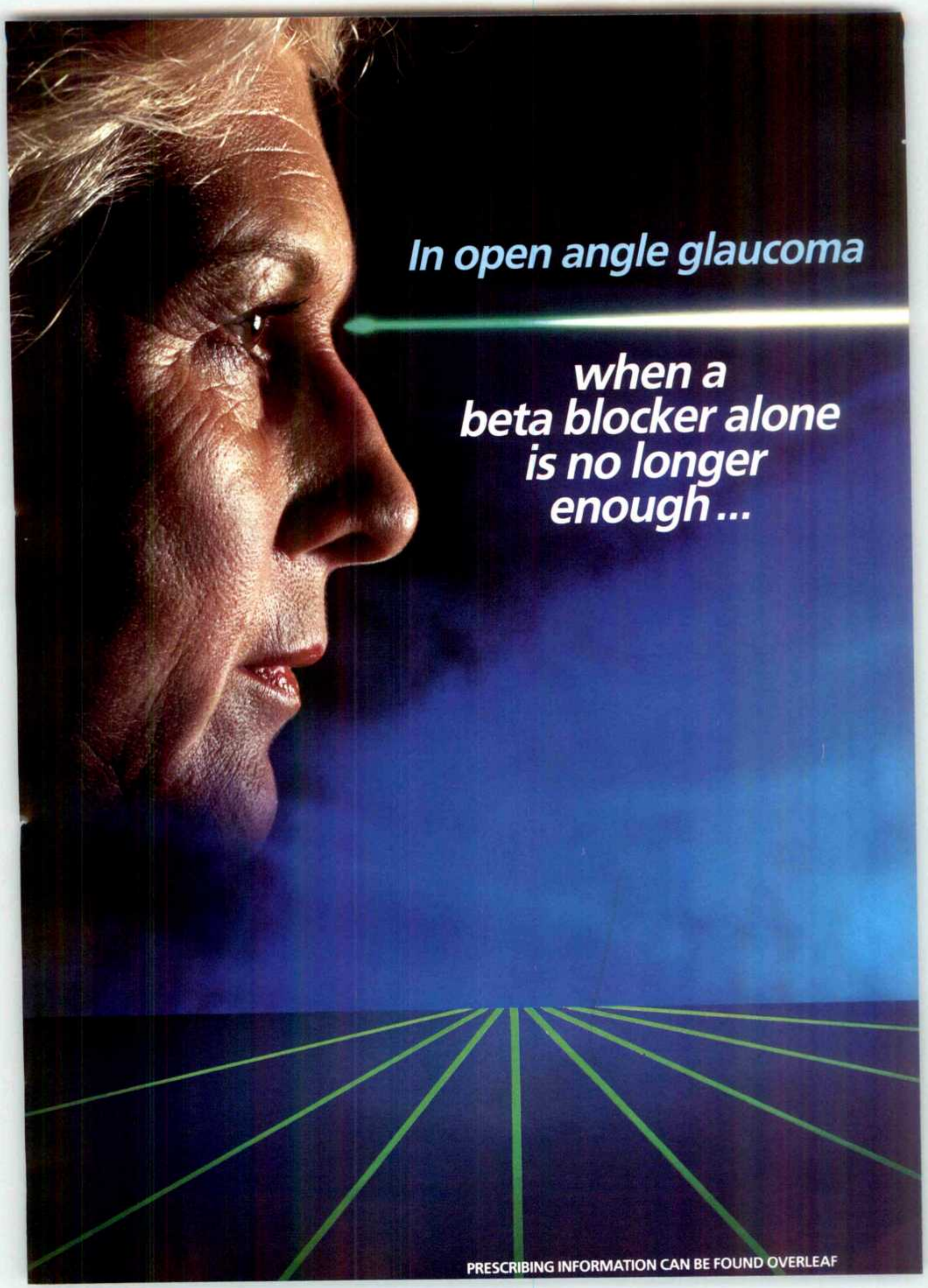
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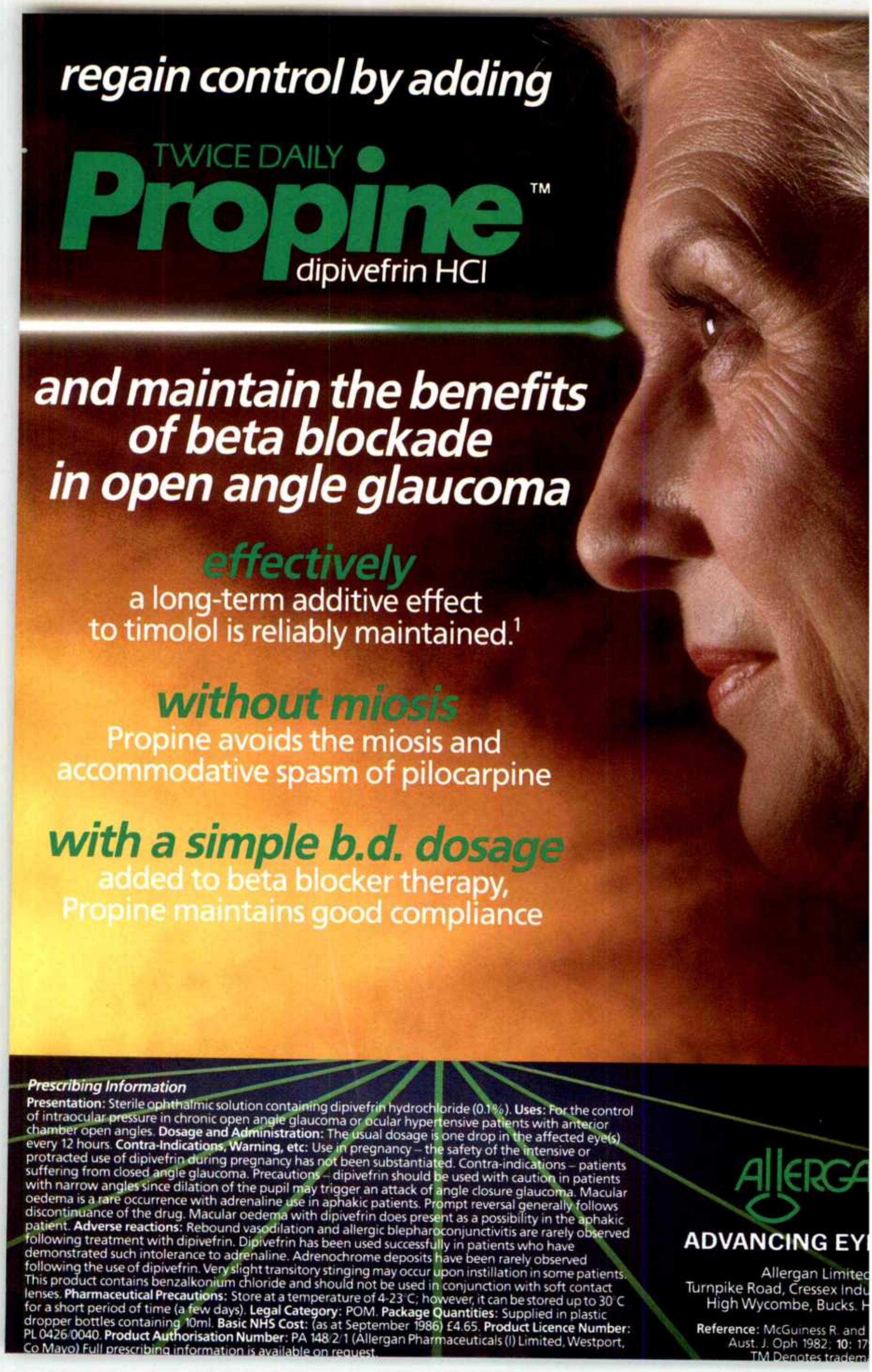

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British Journal of Ophthalmology, 1987, 71, 315-321

Microbiological diagnosis of suppurative keratitis in Bangladesh*

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SUMMARY Experience in setting up an inexpensive microbiology laboratory in the Bangladesh National Society for the Blind Eye Hospital and Training Complex at Chittagong is presented, together with the results of a pilot study to identify organisms responsible in 33 consecutive cases of suppurative keratitis in the Chittagong area of Bangladesh. Of the 33 cases 21 were positively identified by means of Gram stain and/or culture. Two-thirds of the responsible organisms were bacteria, and one-third were fungi. The bacterial causes included *Streptococcus pneumoniae* and *Pseudomonas aeruginosa*. The fungi isolated were *Aspergillus fumigatus*, *Aspergillus ochraceus*, and *Fusarium solani*. Among the causes of failure to diagnose the organism was chronicity of infection and previous treatment. The value of the study in the planning of future treatment regimens, and the implications of setting up similar relatively cheap microbiology laboratory facilities in developing countries, are discussed.

Suppurative keratitis is a common problem in Bangladesh. From a survey by the International Centre for Diarrhoeal Diseases Research, Bangladesh in the rural Matlab area it has been estimated that 230 000 people are blind owing to corneal opacity and that this is mostly due to infection (48%) or injuries (27·5%) (Khan MU, Haque E, Khan MR, report prepared for publication).

Suppurative keratitis in Bangladesh is known to be caused by both bacteria[1] and fungi.[2] As ophthalmic antifungal medications are not available, fungal keratitis is inevitably progressive. In order to manage these cases microbiological diagnosis is required.

Microbiological services are frequently under considerable pressure in developing countries, both because of the numbers of patients and the problems of cost and supply of equipment and trained personnel. Microbiology tests may represent an important item of expense for patients who have to pay for tests done by government hospitals, which normally restrict their services to their own patients.

The Eye Infirmary and Training Complex of the Bangladesh National Society for the Blind (BNSB) is a 120-bed eye hospital at Chittagong which has a continual requirement for microbiological diagnosis, particularly of suppurative keratitis. New patients with suppurative keratitis are seen every day at the BNSB Eye Hospital in Chittagong and in the seven smaller BNSB Base Hospitals in different regions of Bangladesh. These infections are serious problems which threaten eyesight and require hospitalisation for periods averaging 10 weeks (Das A, personal communication). As a result half the eye hospital beds are occupied by patients with frequently intractable infections, particularly during the monsoon period. At harvest time up to 12 patients are seen on some days with corneal injuries and infections related to harvesting or husking rice, and these patients cannot all be admitted. A restricted number of beds imposes limitations on treatment, and many cases are treated as outpatients, it being accepted that the outcome is often hopeless regardless of treatment, particularly in chronic cases suspected of being due to fungi.

A pilot study was undertaken in August 1983 and 1984 to study the aetiology and management of suppurative keratitis, involving the setting up of a

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*A pilot study conducted in Chittagong, Bangladesh, in July, August, September, 1983.

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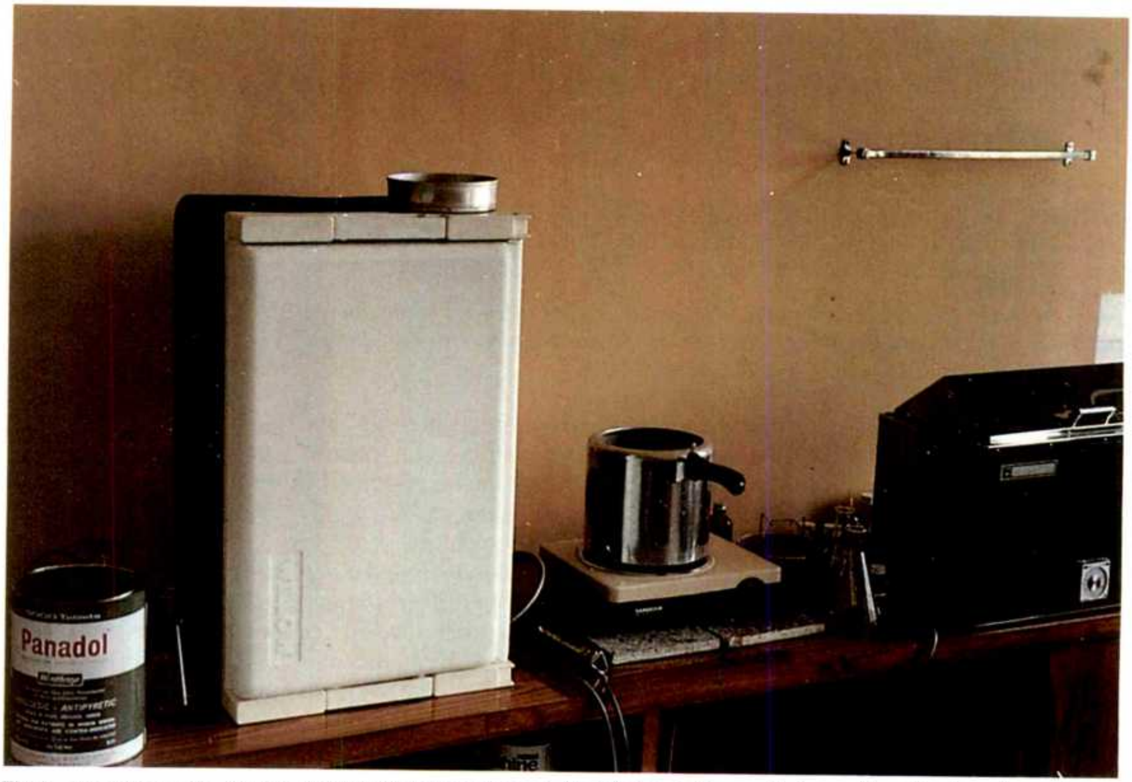

Fig. 1 *Microbiology Laboratory with some of the equipment. From left to right—candle tin used for CO_2-dependent culture; cheap plastic ice box modified with heating element to make an incubator; pressure cooker on a portable electric hot plate; glassware; constant temperature water bath on far right.*

basic microbiology laboratory using cheap readily transportable materials costing a total of 2000 Australian dollars.

Material and methods

EQUIPMENT

The following equipment was purchased in Australia and transported to Bangladesh by courtesy of Thai International Airlines, who made no charge for their services. Some of the laboratory equipment is illustrated in Fig. 1.

An incubator was constructed from a lightweight plastic cooling box with a hinged door (Vacationer made by Willow, Australia). The Anax Company assembled a 300 watt mica heating element controlled at 36°C by a solid state thermostat and monitor (PM4 made by RKC) with a second thermostat (Robertshaw) set to cut out at 38°C as a back-up. A pressure cooker was heated on a portable hot plate (Kambrook) to autoclave culture media and other materials. A binocular microscope with built-in illumination (Olympus CHB) was used. Other equipment included the following: Bunsen burner and butane canisters (Pongrass); glass Petri dishes for agar cultures; McCartney bottles (30 ml) for Sabouraud's agar slopes; reagents for Gram, Giemsa, Ziehl-Neelsen, and methenamine silver stains; beam balance and weights; conical flasks; bacteriological wire loops; thermometer; glass slides; Coplin jars; staining bottles; dehydrated culture media (Gibco); dehydrated rabbit plasma; antibiotic sensitivity test discs (Oxoid Multodiscs).

STAFF

A paramedic was selected (author AH) from the hospital staff, and after nine months' experience in the laboratory was brought to Australia for 12 months' training. During the 12 months he attended full time the Microbiology Department at Liverpool Hospital, under the direction of author GW and spent time at Sydney Eye Hospital, and completed his training by spending a month with Professor Coster's Department in Flinders Medical Centre, South Australia.

During the evening while in Sydney he attended a course at the Sydney Technical College earning distinctions in microbiology and a certificate of competence.

LABORATORY METHODS

Stains were prepared by standard methods with distilled water supplied by Glaxo Company in Chittagong. Dry media bases were reconstituted with tap water and autoclaved in the pressure cooker for 15 minutes. Trypticase soy agar was used as recommended by the manufacturer (Gibco) with the addition of 2 g of yeast extract per litre (as suggested by Mr L Taylor, University of Sydney). A beam balance and set of weights was used for weighing media and stains. Blood was obtained from sheep purchased locally and grazed at the hospital. Wool over the neck was clipped and the area swabbed with alcoholic iodine. Blood was aspirated while the vein was dilated by pressure lower on the neck. Blood was defibrinated by mixing with sterile glass beads for five minutes. The beads could be separated from the fibrin and reused. Blood was added to sterilised media cooled to about 50°C to a proportion of about 10%. For chocolate agar the media were reheated to 80°C after addition of blood for about five minutes or until chocolate brown. Vitox, a vitamin and amino acid supplement (Oxoid), was added to some batches to enhance isolation of *Haemophilus influenzae (H. aegyptius)* from eye specimens. Poured plates were wrapped in plastic and stored in a refrigerator. The quality of media was checked by culture of *Streptococcus pneumoniae* on blood agar and *Haemophilus influenzae* on chocolate agar. These bacteria grew well on the respective media.

Corneal scrapings were plated directly on to agar plates and smeared on to glass slides for staining. Smears were stained routinely by Gram stain. Methenamine silver could be used to restain negative smears for improved detection of fungi.

Sabouraud's slopes were inoculated by several separate strokes to mark but not break the agar so that subsequent growth from the inoculum could be distinguished from contaminants not on the mark.[3] Sabouraud's slopes were sealed with screw caps to prevent dehydration or contamination incubated at room temperature and were examined daily for three weeks.

Blood and chocolate agar in Petri dishes were inoculated and then streaked out with a sterile wire loop and incubated at 37°C in a candle tin.

Bacteria and fungi were identified by standard methods using colony morphology, Gram stain, and basic tests. *Staph. aureus* was identified by coagulase testing using human or rabbit plasma; *Str. pyogenes* by bacitracin sensitivity, morphology, Gram stain, and catalase; pneumococcus by optochin sensitivity; and Gram negative rods by decarboxylase, sugar fermentation, Voges-Proskauer, indole, urea and citrate tests as provided in the API identification kit 20E or the Microbact 12E test tray (Diagnostic Products, Adelaide, SA).

Haemophilus influenzae was identified by growth on chocolate agar and growth around combined X and V factor discs on nutrient agar. *Pseudomonas aeruginosa* was identified by characteristic colouring morphology, pigment production, and oxidase test. Fungi were identified by morphological criteria. Antibiotic disc diffusion sensitivity tests were performed by the calibrated dichotomous sensitivity method[4] on Sensitest agar. Gram stain was used alone for eight patients, of whom two had pneumococcal like bacteria and three had Gram-negative rods in scrapings from corneal ulcers.

PATIENTS

Thirty-three patients with corneal ulceration were examined over a period of three months. Histories were taken, and the eyes examined with the aid of a slit-lamp. Five of the patients had been in hospital for an average of 3·5 weeks each.

CLINICAL METHODS

Specimens were taken from the cornea by carefully scraping the ulcer with a Kimura platinum spatula (OPSM) or a sterile Bard-Parker scalpel blade. The first specimen was taken for culture and without local anaesthetic.

The patients with pneumococcal infection were treated with hourly irrigations of a penicillin solution, 200 units/ml in normal saline, administered with an intravenous giving set. Chloramphenicol ointment was used at night and penicillin 0·5 million units given subconjunctivally for four days as well as penicillin orally.

The *Pseudomonas* and other Gram-negative rod infections were treated with 1% gentamicin drops hourly, gentamicin 20 mg subconjunctivally daily for four days, and polymyxin-oxytetracycline ointment at night.

The fungal ulcers were treated with 1% miconazole (10 mg/ml) drops second hourly,[5] or in the case of *Fusarium solani*, which appears resistant to miconazole in vitro, pimafucin (Natamycin) drops 2·5% (25 mg/ml) were given second hourly. Miconazole was also given as subconjunctival injections of 10 mg daily for four days, with additional subconjunctival injections later in some cases.

EPIDEMIOLOGY

Sixteen rice grains from a batch of stored rice were cultured, eight on Sabouraud's agar and eight on blood agar, in an attempt to detect potential pathogens. Seven samples of pond water and three samples of canal water from the Chittagong area were cultured on blood and Sabouraud's agar before and after 10-fold concentration by centrifugation and colonies were enumerated approximately.

Conjunctival swabs were taken from healthy untreated eyes of four nursing staff and six cataract patients and cultured on blood and chocolate agar. Nasal swabs were taken from four doctors, four nursing staff, and eight patients and cultures examined for staphylococcal colonies. These were tested by slide coagulase to identify *Staph. aureus*.

Results*

The lightweight incubator functioned well with steady uniform temperature maintenance at 35°C. The media made with tap water grew fastidious pathogens such as *Str. pneumoniae* and *Haemophilus influenzae*, including strains isolated directly from patients' eyes. The availability of small quantities of distilled water was necessary for preparing stains, but untreated tap water proved satisfactory for media and for washing slides.

The Gram stain proved adequate to detect fungi in those cases from which they were isolated, the main factor affecting detection being the adequacy of the scraping taken with the platinum spatula. It was noticed particularly with bacterial ulcers that organisms were best detected from the scrapings of the cornea itself, and were frequently absent from the loose exudate overlying ulcers.

Contamination of agar plates with airborne bacteria or fungi could be distinguished from growth from the patient's specimen by the relationship of the colonies to the inoculating streak. That is, growth along the streaks was related to the patient, while growth away from the streaks was due to contamination. Airborne bacteria and fungi were relatively more common in Chittagong than in Sydney.

A history of initiating trauma was obtained in 14 of the 29 patients with suppurative keratitis. The commonest trauma was due to the husk of the rice grain flying into the eye during the process of beating the rice to remove the husks—that is, 'paddy injury'—which was reported in seven cases. Other causes of trauma included sand (two boys), a date palm, a wooden stick, a bamboo splinter, and a needle. In the case of the pseudomonas keratitis, the cause was thought to be almost certainly due to contaminated water with which the injured eye was initially washed.

Scrapings taken from corneal ulcers of the 29 patients with suppurative keratitis revealed the following organisms in Gram stains and cultures (Table 1).

Gram stains and cultures did not reveal any significant micro-organisms in the other patients, though two had been treated in hospital for two and four weeks and others had purchased ointments, which probably included antibiotics in many cases, before coming to the BNSB Eye Infirmary.

Interestingly in three cases Gram stains revealed Gram-intermediate (i.e., pinky-blue) curved rods in corneal ulcer scrapings. They were found in cases of pneumococcal ulcer and in one case where only symbiotic *Corynebacterium* xerosis was isolated in culture. They were also seen in a smear from another

Table 1 *Organisms detected*

Organism	*Number of Patients*
Bacteria	
Streptococcus pneumoniae	5
Pseudomonas aeruginosa	3
Staphylococcus epidermidis	3
Enterobacter	1
Providencia	1
Unidentified Gram-negative rods	3
Corynebacterium (normal flora)	2
Fungi	
Aspergillus fumigatus (Fig. 2)	1
Aspergillus ochraceus	1
Fusarium solani (Fig. 3)	1
Unidentified filamentous fungi	4

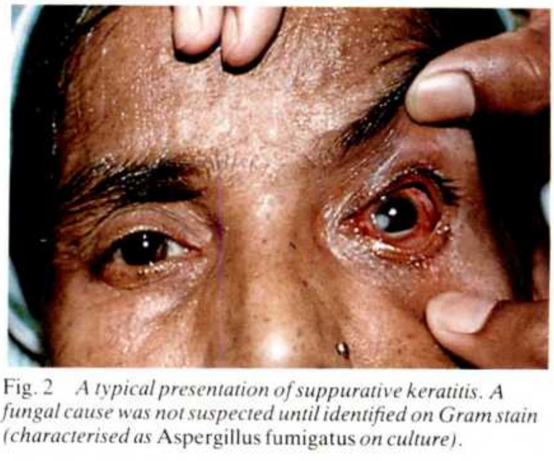

Fig. 2 *A typical presentation of suppurative keratitis. A fungal cause was not suspected until identified on Gram stain (characterised as* Aspergillus fumigatus *on culture).*

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*During the period of study four additional patients were noted attending the hospital with recurrent herpes simplex keratitis with typical dendritic ulcers revealed by fluorescein staining in two cases and a geographic ulcer in a third case previously treated with steroid-containing ointment, which is freely obtainable in the smallest of villages throughout Bangladesh. These patients were treated with vidarabine or idoxuridine ointment. Another inpatient, a young woman, had bilateral corneal scars with a history of recurrent ulceration self treated with steroids which was related to a history of cold sores on the mouth.

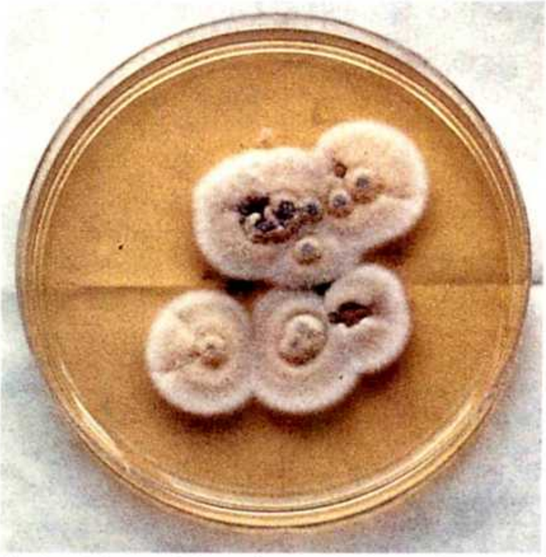

Fig. 3 *Culture on Sabaraud's agar of colonies of* Fusarium solani.

patient who had been in hospital for six weeks from whom a fungus was isolated which could not subsequently be identified owing to overgrowth by a contaminating fungus. No such bacteria could be grown in culture, though anaerobic cultures were not done and the organisms were reminiscent of the appearance of *Mobiluncus*, which is a Gram-variable anaerobic curved rod implicated as a cause of vaginosis.[6]

Also seen in Gram stains of scrapings from three patients were yeast-like organisms with capsules staining Gram-negative which did not grow in culture and were presumed to be *Pityrosporum orbiculare*. This is a yeast-type fungus associated particularly with seborrhoeic dermatitis and probably coming from the eyelashes as a harmless saphrophyte.[7] The patients mostly presented late with advanced corneal ulcers, and the appearance of the ulcer was not helpful in the differential diagnosis of bacterial and fungal infection. The commonest initiating trauma for corneal ulcers was due to husking rice (paddy injury). Among the patients in whom fungi were found, only one had a history of paddy injury compared with four of 14 with bacterial infection. However, paddy grain injury was not associated with pneumococcal infection. Hence there was little in the history of patient characteristics to point to fungal or bacterial infections, except a longer history in some of the cases of fungal ulcers. Even the duration of ulceration prior to presentation was often similar in the fungal and bacterial cases, though four of the patients with fungal ulcers spent an average of 3·5 weeks in hospital receiving antibacterial therapy before this project started (Table 2).

Table 2 *Comparison of fungal and bacterial infections*

Fungi	*Bacterial*
Total 7	14
Injury 1 (paddy grain)	7 (4 paddy grain)
Male/female (4/3)	12/2
Average duration* 2·3 weeks before presentation	11 days
Average age 50 years	30 years

*The duration before presentation was estimated from the time of injury if the patient could recall it, or was based on the duration of patients symptoms. The onset of symptoms in the bacterial cases tended to be more severe and resulted in early presentation.

The ulcers showed steady improvement with the treatment regimens described despite their advanced pathology at presentation, and all patients but one, who had the affected eye enucleated, were discharged with the disease apparently arrested.

EPIDEMIOLOGY RESULTS

All eight stored rice grains cultured on Sabouraud's agar and blood agar grew *Bacillus* species and six of the eight on Sabouraud's agar grew fungi of the family *Mucorales*. Five of the eight also grew a yellow *Aspergillus* species similar to that isolated from one patient. Two other unidentified fungi were also seen in the cultures.

Samples of pond and canal water, which are often used to wash injured eyes, were cultured. An average of 10^3 to 10^5 bacteria per ml were found, including Gram-negative rods in eight of 10 samples, yeast in two, and *Bacillus* species in two.

Conjunctival swabs from four healthy staff and six uninfected patients revealed occasional *Staph. epidermidis* in six and *Corynebacterium* species in two cases and, interestingly, *Haemophilus influenzae* in one outpatient presenting for refraction. A survey for *Staph. aureus* carriers revealed positive nose swabs from two of four doctors, one of four nursing staff or paramedics, and two of eight patients. All five isolates of *Staph. aureus* were resistant to penicillin.

Discussion

Our experience confirms that fungi are an important cause of suppurative keratitis in Bangladesh, accounting for some 30% of the cases of suppurative keratitis in this study. Furthermore we have found that there is a variety of fungi involved reminiscent of the diversity of genera found in (sub) tropical areas in the USA and elsewhere.[8] In Florida the commonest cause of fungal ulceration is *Fusarium solani*, which has not previously been well recognised as a cause in Bangladesh. Also *Aspergillus fumigatus* and *Aspergillus flavus* and many other fungi have been reported in other countries. We found *Aspergillus* *fumigatus* as previously reported in Bangladesh[3] and a sulphur yellow species that was probably *Aspergillus ochraceus*. This yellow species was also isolated from rice grains and may be common in the environment.

The pathogenesis of fungal keratitis is unclear. Trauma is assumed to be an initiating factor, though usually, as in our cases, there is no clear incident of injury.[8] Bacterial and fungal organisms growing in the thatch of houses have been implicated as causing allergic pneumonia to people living in warm climates.[9] Environmental cultures from dwellings of patients with fungal ulcers might be of interest, though two small random samples of thatch did not reveal fungi in this study.

The significance of the finding of fungi as a cause of suppurative keratitis is important when it is appreciated that antifungal therapy for suppurative keratitis is not freely available in Bangladesh. Furthermore, the problem of suppurative keratitis due to fungi is aggravated by the fact that corticosteroid ointments are freely available in the villages.

We found the Gram stain alone was of value in making a diagnosis of bacterial or fungal keratitis. In an extended study to look at this question we found that in a series of 66 cultures 58 were culture-positive for bacterial or fungal organisms, and, of these, 47 were anticipated on Gram stain examination alone.

Establishing the pattern of infective organisms causing suppurative keratitis was fundamental to developing appropriate treatment protocols. These protocols are referred to above in clinical methods. The results of these therapeutic regimens was one of resolution and healing in those cases with proved microbiological diagnosis, except for one case of pseudomonas infection which was too advanced at presentation and resulted in perforation of the cornea soon after treatment began. The fungal infections were treated with topical and subconjunctival miconazole, and this therapy was effective except in one case due to fusarium, which is known to be resistant to miconazole.

The frequency of *Str. pneumoniae* as a cause of corneal ulcers is of interest. In contrast to some reports[10] a history of trauma was not obtained from many of our patients with pneumococcal ulcers. It is likely that many patients have pneumococcal colonisation of the throat and/or conjunctiva and that only occasionally the more virulent capsular serotypes of pneumococci, such as type 4, cause keratitis.

The role of the coagulase-negative staphylococci grouped here as *Staph. epidermidis* in the corneal ulcers from which they were isolated is uncertain. These organisms are now separated into several species of varying degrees of parasitism.[11] However, some strains of *Staph. epidermidis* have been implicated in the pathogenesis of keratitis by their production of toxins.[12]

The isolation of *Providencia* species from the eye of a young child who had measles, gastroenteritis, and keratomalacia may represent an opportunistic relatively less virulent colonisation of an already damaged eye. The relatively high levels of environmental bacteria in canal and pond water suggest the likelihood of such water, which is needed for washing, as a source of colonisation of the injured cornea. Traditional eye treatments may also contribute.[13]

The finding of *Pseudomonas aeruginosa* in a patient with rapidly progressive keratitis reinforces the necessity for vigilance in the case of solutions that might be used to wash foreign bodies from eyes. The rapid progression of this infection depends on proteinases produced by the organisms,[14] though the exotoxin A appears important.[15] It is of interest that pseudomonas elastase is a metallo-proteinase, as are collagenases, including that of neutrophils[16] [17] that are inhibited by tetracycline, which binds the metallic radical in the enzyme. Thus the combination of polymyxin with oxytetracycline (Terramycin), which is the routine ointment for eye infections at BNSB hospitals, may be appropriate for pseudomonas keratitis, though the elastase enzyme appears to be less important than the alkaline protease.[15] However, tetracycline is synergistic with amphotericin B against *Aspergillus* species.[18] Thus the addition of pimaricin (which is related to amphotericin) to treatment with polymyxin-oxytetracycline may provide good antifungal prophylactic therapy.

Treatment regimens effective in this pilot study, including antifungal therapy with subconjunctival miconazole, yielded results that in our opinion are deserving of further study.

In conclusion we believe this work confirms the feasibility of setting up similar relatively cheap microbiology laboratory facilities to develop strategies for the treatment of suppurative keratitis, and to help reduce avoidable blindness in developing countries. The total cost of equipment, setting up the laboratory, and training of the microbiologist was approximately 10 000 Australian dollars. Short of this, merely the facilities for doing Gram stain identification will allow appropriate treatment in the majority of cases, which will subsequently be shown to be positive to culture. The addition of this skill to the base hospitals in rural areas of Bangladesh is proposed with the Chittagong Eye Hospital and Training Complex remaining as the reference centre for problem cases.

A further study of treatment regimens will be the subject of another report when larger numbers of cases are available.*

*Following the setting up of this laboratory in 1983–4 Dr A Richards and Dr E D Wright brought protocols to Chittagong which modified the treatment regimens outlined. These protocols are being filled in by the staff of the laboratory, and this material will be the subject of a future joint publication.

Foresight Australia funded the microbiology laboratory in Chittagong, and the training of A Howlader in Sydney. Thai International Airlines transported laboratory equipment from Sydney to Bangladesh without charge. Professor Y E Cossart and Mr L Taylor, of the Department of Infectious Diseases, University of Sydney, provided considerable assistance and advice. Medications were donated by Roussel Pharmaceuticals, Allergan, and Astra Pharmaceuticals and the Sydney Eye Hospital.

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Correspondence

Screening for visual defects in preschoolchildren

SIR, I would like to comment briefly on the paper by Ingram *et al.*, 'Screening for visual defects in preschoolchildren.'[1] Dr Ingram and his associates continue to raise important questions and make excellent empirical contributions to the often difficult–to–study area of child vision screening. They also have been careful in the present report to qualify their findings in several respects. Nonetheless, in view of the strong statement of there being 'no evidence' (p. 16) to support the need for preschool screening, some further comment seems appropriate.

More than a quarter of the population studied (26%, Table 1) had a condition of abnormal vision detected prior to the study's screening. Since this group presumably presented with the most serious and hence most readily detected abnormalities, they would represent the most important target group in an unselected population screening. In effect removing them from the screening sample of the present study thus limited the study population to the less serious, and hence less important to detect and treat, segment of the abnormal vision subpopulation. This limitation is an important one, because whether this pre-screening detected group would have been detected without screening in other socioeconomic or eye care delivery conditions than applied to this study is an open question. In one large-scale survey of 12–17 year olds in the USA, for instance, less than a third of the individuals detected with strabismus indicated any history of treatment.[2]

Of those who presented with visual problems after the screening at age 3½, 43% apparently passed the screening and are therefore classified as "false negatives" of vision screening (p. 18). Under-referral is, of course, a serious matter for a screening programme for both credibility and medicolegal reasons.[3] It thus seems important to emphasise that this false negative rate was derived, not from vision screening generically, but from the particular screening methodology used in this study, which comprised cover test, acuity, and retinoscopy. The shortcomings of all three at detecting both amblyopia and strabismus have been discussed elsewhere,[3 4] and Dr Ingram and his associates in their own findings have pointed up the shortcomings of refraction in detecting strabismus.[5 6]

Broader conclusions about screening utility would have been justified if a reliable measure of binocular visual function had been included, in view of other evidence of such measures' effectiveness in screening.[3 4 7–9] An attempt was made to use the RDE random dot stereotest, but this was abandoned since the test was found to be 'unreliable' (p. 18), and a large proportion–22%–of the children tested were reported as not attempting the test or guessing.[1] Unfortunately, no details are reported on details of the test administration methodology or the nature of this unreliability, which makes detailed comment impossible. In view of my own involvement in the development of this particular test I do not wish to appear partisan. However, it does seem fair to point out that studies by others as well as myself have found the RDE to be quite reliable and easy to use with young children.[3 7 9–13] Guessing certainly should not have been a problem if there were adequate repetitions and the test plates not marred so as to provide a nonstereoscopic cue to children. Furthermore, it is not clear why another stereotest such as the TNO[8 14 15] or right hand plate of the Randot II[14] was not substituted if the RDE was not found to be satisfactory.

Finally, the rationale for screening for amblyopia is challenged on the basis that only 3/16 of the detected patients achieved 6/6 vision from occlusion (Fig. 1), an outcome termed 'not very encouraging' (p. 20). Exactly the opposite point of view could be supported, however–that the outcome was in fact encouraging and the screening thus justified–on the basis of the fact that 15/16 patients did show *some* improvement from occlusion (Fig. 1). Indeed, if only a 6/6 result is considered adequate, much of the standard clinical treatment of amblyopia must be questioned.

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Sir, Thank you for allowing me the opportunity to reply to Dr Simons's letter. Perhaps I may answer, one by one, the points he raises.

Firstly, we cannot say that those in our sample who presented before 3½, almost inevitably with a cosmetically noticeable squint, would necessarily have done so in other socioeconomic conditions. The particular set-up we have in that part of our district could have predisposed us to the findings we reported.

Secondly, I accept that our 'false negative' rate was derived from the screening methods we used. 26% of those ultimately found to have abnormal vision had a 'false normal' visual acuity and/or cover test when screened at 3½. Likewise, 20% of those ultimately found to have abnormal vision, had a 'normal' refraction at 3½ and would have been 'missed' by this test.

The question of 'false positives' is equally important, because they cause increased and unnecessary parental concern, work and financial expense. In our series 56·7% of those who recorded abnormal or uncertain vision at 3½, and 51·2% of those who had an abnormal refraction (using our criteria) at 3½, actually had normal vision without any treatment. The majority of the 'false abnormal' refractions were hypermetropia without astigmatism or anisometropia. I have since realised that, if we had chosen only astigmatism and/or anisometropia as the criterion for abnormal refraction, the percentage of false positives using refraction would have been reduced to 29·5%. If we had combined this with a cover test, I calculate we would have identified 85% of those with abnormal vision (excluding myopia). It might be possible to simultaneously test for an abnormal refraction and squint using the more modern developments of photo refraction. Nevertheless, some false positives and false negatives are both inevitable whatever method is used.

Thirdly, Dr Simons justifiably questions our method for stereoacuity testing. Maybe guessing and inadequate cooperation should not have been a problem, but they were. We found interpretation of the response to be too unreliable for use as a one-off, non-repeated screening test in the population sample we screened. This does not mean to say that others would also find this so.

I will admit to being slightly 'partisan' against testing for stereoacuity, but no more than I am against any other 'subjective' screening test. This is because in most cases defective visual acuity is associated with an abnormal refraction and/or a squint, and therefore I think that an objective test *should* be more accurate than a subjective one, particularly in preschool children. Having said that, we have not recommended screening by refraction–we merely advised against screening at 3½ by any method.

Finally, our views on the results of occlusion in these children are questioned again. I do not think that improvement to 6/6 is necessary before one can conclude that occlusion has been valuable. However, I wonder whether one or two lines improvement *in the range 6/18 to 6/9* is worthwhile, and I do believe that the standard treatment of amblyopia should be questioned.[1] R M INGRAM

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Reference

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Adverse reactions to guanethidine eye drops

Sir, I write to express my regret that guanethidine 5% with adrenaline 1% eyedrops have been voluntarily withdrawn by the company responsible for their manufacture.

I have for some years been concerned about the rare effects of antiglaucoma medication and other topical eye therapy on the conjunctiva and cornea.[1 2] There is no question that these adverse effects are rare, unpredictable, and not normally dose or time related.

All topical therapy, in common with other medicines, carries both benefit and risk, and it is the job of the prescriber to calculate this risk/benefit ratio for any patient receiving treatment. I understand that at least 1000 patients whose glaucoma was currently controlled with guanethidine 5% plus adrenaline 1% have now been deprived of useful therapy. I believe that it would have been more appropriate for the company to insert a warning in the package advising that the combination had been associated with conjunctival cicatrisation and advising that prescribers should monitor the outer eyes of patients receiving drops. In addition to depriving a large number of patients of useful treatment the decision to withdraw the drops also creates an unreal impression of safety. Any topical therapy can produce an unaccepted adverse reaction, and all prescribers will need to continue to watch for signs of these adverse effects, which are not limited to guanethidine and may even be associated with common constituents such as preservatives.

Responsibility for monitoring adverse effects as well as benefits will always be the prime duties of a prescribing doctor. PETER WRIGHT

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Book reviews

Neuro-Ophthalmology: Clinical Signs and Symptoms. 2nd edn. By Thomas J Walsh. Pp. 499. US$52·25. Lea and Febiger: Philadelphia. 1985.

This book was first published in 1978 and the revised edition includes chapters by a number of authorities to augment the author's clinical experience. The chapters are generally arranged under symptoms, and they include ptosis, diplopia, blurred vision, and headache. Other chapters consider signs such as papilloedema, exophthalmos, and pupillary abnormalities. Finally there are chapters on chromosomes, facial palsy, and electrodiagnosis.

The section on CT scanning in neuro-ophthalmology has been expanded. This is a compact and valuable book on neuro-ophthalmology. M D SANDERS

Embryologié et Tératologie de l'Oeil. By G OFFRET, P DHERMY, H OFFRET. Pp. 296. 490F. Masson: Paris. 1985.

After discussing briefly the main stages of embryogenesis the authors discuss the development of the various structures of the eye and adnexa. There follows a discussion of teratogenesis, experimental ocular teratology, and human ocular teratology. If you want an up-to-date account of ocular embryology and teratology in French, this is the book to be recommended. BARRIE JAY

Genetic Biochemical Disorders. By PHILIP F BENSON AND ANTHONY H FENSOM. Pp. 692. £55·00. Oxford University Press: Oxford. 1985.

This is the twelfth Oxford Monograph on Medical Genetics and covers concisely the very large field of genetically determined biochemical disorders. After a short introduction there are sections on the mucopolysaccharidoses, disorders of glycoprotein metabolism, the sphingolipidoses, disorders of aminoacid metabolism, organic acidaemias, disorders of purine and pyrimidine metabolism, disorders of carbohydrate metabolism, erythrocyte enzyme deficiencies and haemolytic anaemias, disorders of porphyrin and haem, disorders of steroid metabolism, disorders of lipoprotein metabolism, disorders of thyroid hormones, and disorders of copper metabolism. In view of this very extensive list of contents it is not surprising that the clinical, genetic, pathological, and biochemical features of each disorder are treated in a very succinct manner, often with emphasis on prenatal diagnosis and genetic counselling. Most of the ocular manifestations of each disease are mentioned, albeit briefly. It is disappointing that, for a book published in 1985, there appear to be relatively few references after 1980, despite the enormous advances in molecular genetics over the past few years. This is a useful (relatively) small reference book which should be available to all ophthalmologists seeing patients with the rarer genetically determined biochemical disorders. It will have to be used with care in view of the considerable advances in this field occurring almost daily. BARRIE JAY

Burian-Von Noorden's Binocular Vision and Ocular Motility. 3rd edn. By GUNTER K VON NOORDEN. Pp. 500. £77·00. Blackwell: Oxford. 1985.

This book first appeared in 1974 and immediately became a classic text on its subject. Sadly, Hermann Burian died in the year of the first edition, but Professor Von Noorden has soldiered on valiantly with the two subsequent editions, of which this is the latest.

The book is divided into four sections—on the sensorimotor physiology of the eyes, the neuromuscular anomalies of the eyes, clinical characteristics of these anomalies, and finally principles of therapy. It is very difficult to fault the book. It has always been the best balanced and most impartial source of data where other authors have a tendency to ride hobby horses. The reader is particularly directed to the sections on exotropia, microtropia, and the surgical treatment of congenital esotropia. In addition each chapter has an enormous number of useful references with a full list at the end of each chapter. I had a few disagreements: in chapter 24 the original Harada-Ito procedure to correct excyclotropia is correctly described, but there is no mention of the Fells modification, which is the technique used by the majority of squint surgeons. Although the technique of botulinum toxin treatment of strabismus originated by Alan Scott is relatively new, it has been practised with considerable success since 1979 by an increasing number of investigators, and it would be hard to discover that from the 13 lines in which the technique is described.

However, apart from these minor points this is a splendidly comprehensive book which must be in every eye department library and which can be warmly recommended to any young ophthalmologist in training or who requires to read for the fellowship examination. J P LEE

Notes

Finance offered

David Cole Travel Fellowship

The David Cole Travel fellowship, instituted by Merck Sharp and Dohme in memory of Professor David Cole, will assist a visit to a hospital or research centre during the academic year starting 1 October 1987. The award will be equivalent to £2000. The purpose of the award is to enable the successful applicant to gain experience and knowledge in pursuit of a specific project related to glaucoma.

Glaucoma Group Research Grant

The Glaucoma Group Research Grant, sponsored by International Glaucoma Association, will be available for a research project clinically orientated towards glaucoma for 1987. The award will be equivalent to £2000. The Grant may be used towards salary or project expenses or for buying equipment.

Both these awards are available to medical graduates and non-medical scientists resident in the United Kingdom or the Irish Republic. They may be held concurrently with other awards. Further details and application forms from Dr S Nagasubramanian, Secretary Glaucoma Group, Glaucoma Unit, Moorfields Eye Hospital, High Holborn, London WC1V 7AN. The closing date for applications is 19 June 1987. The successful candidate will be informed by August 1987.

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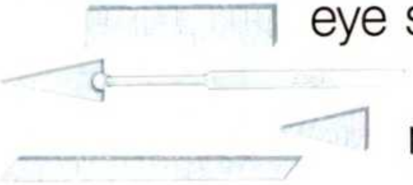

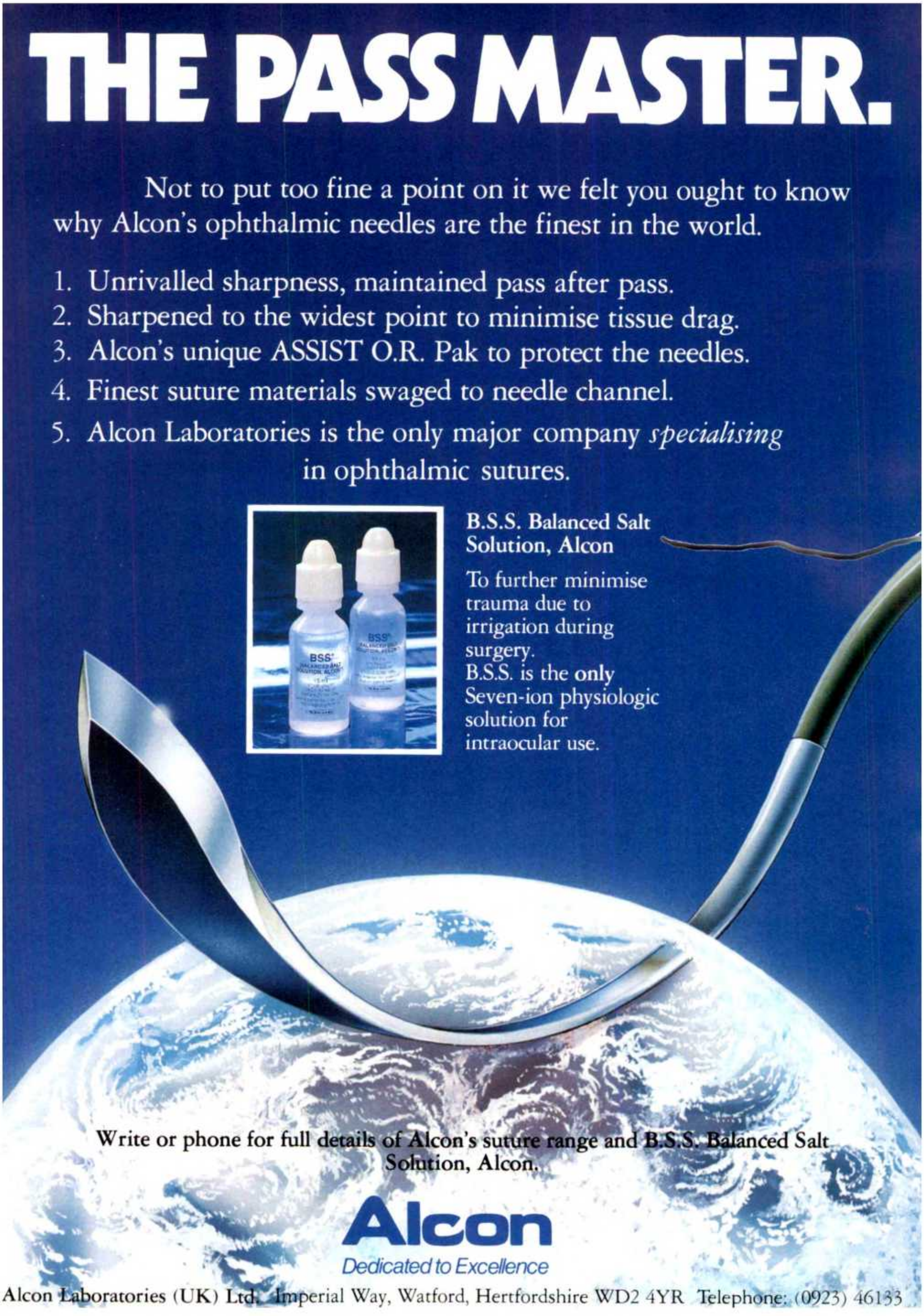

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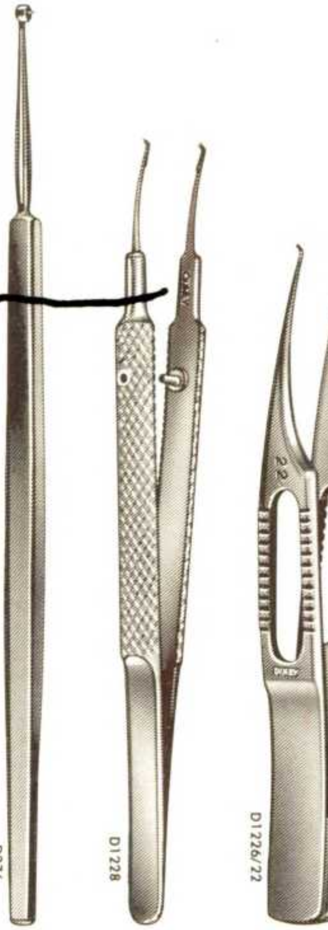

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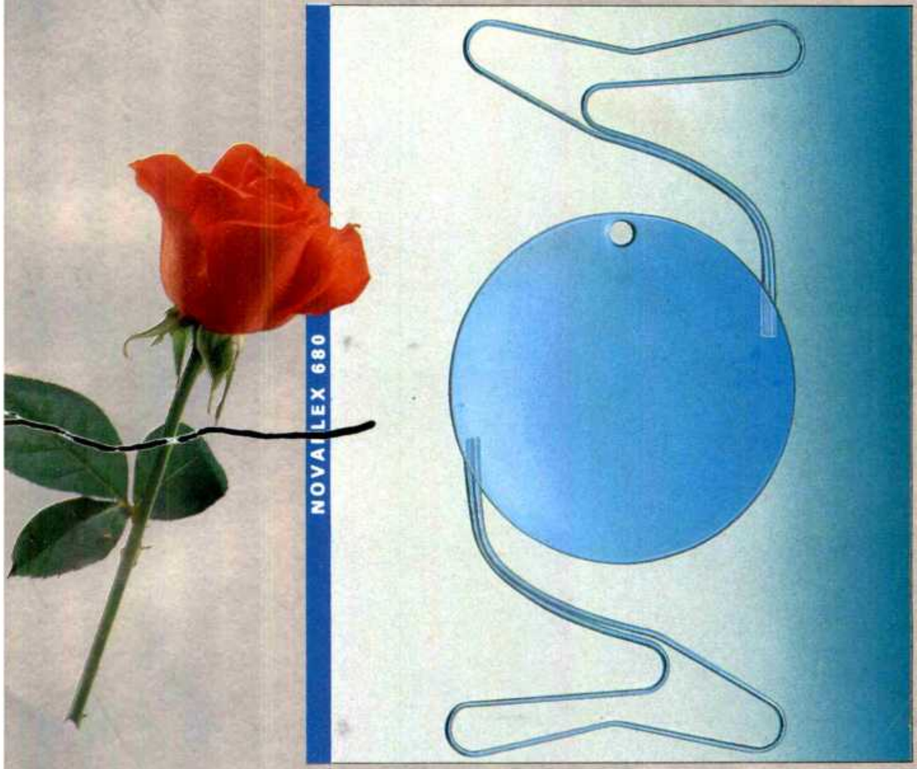

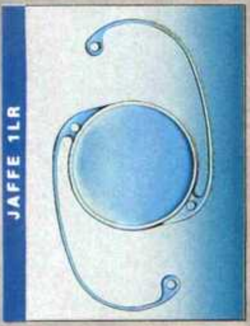

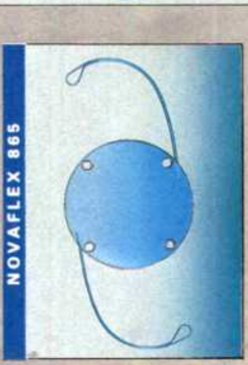

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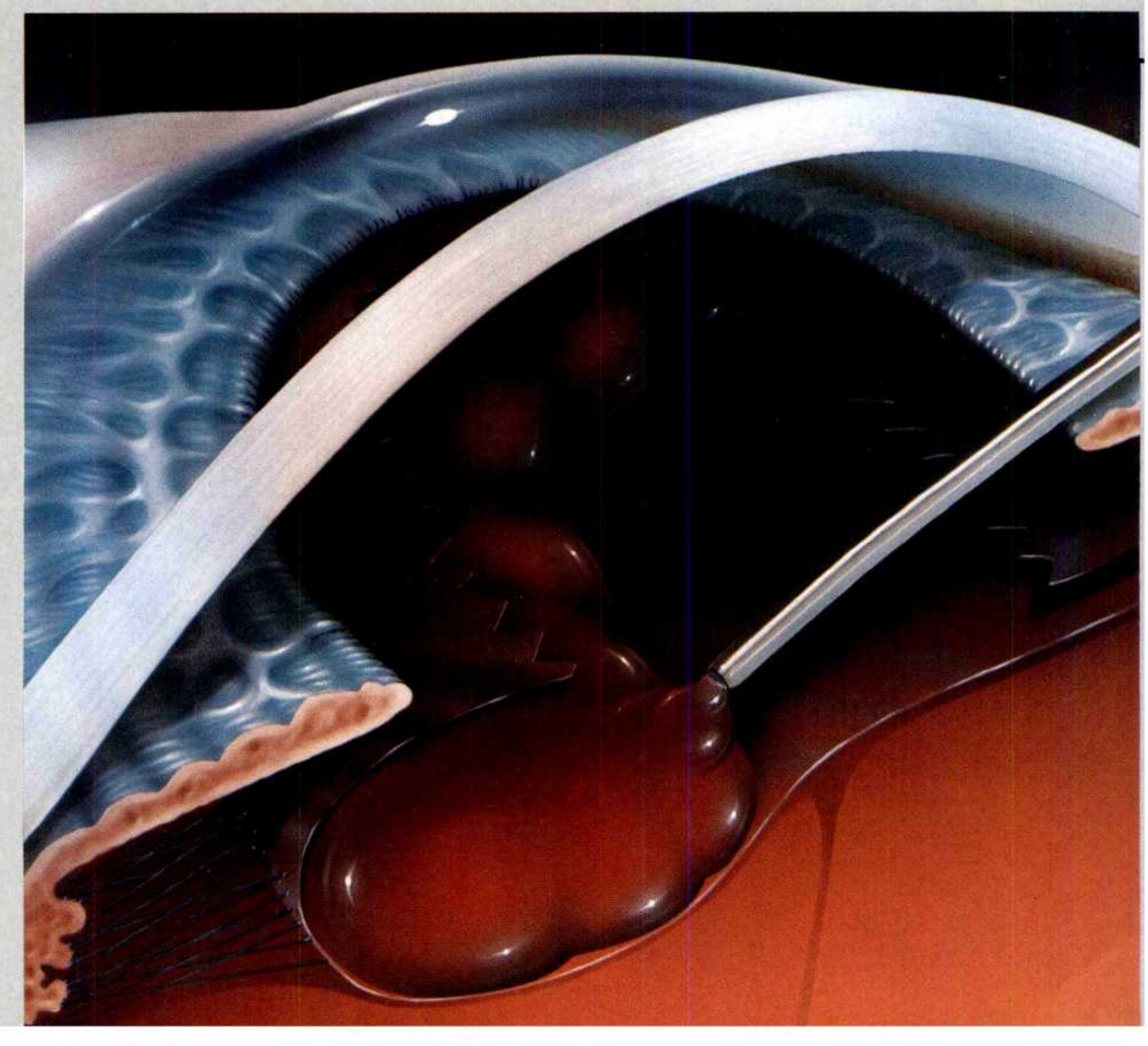

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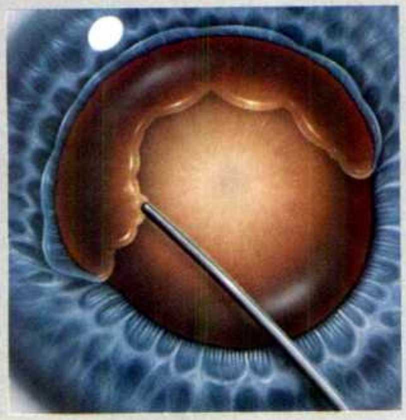

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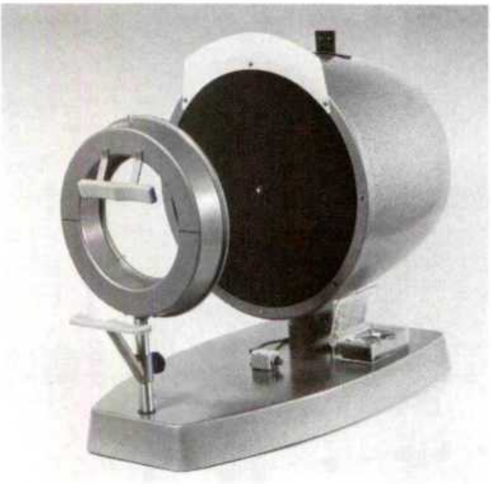

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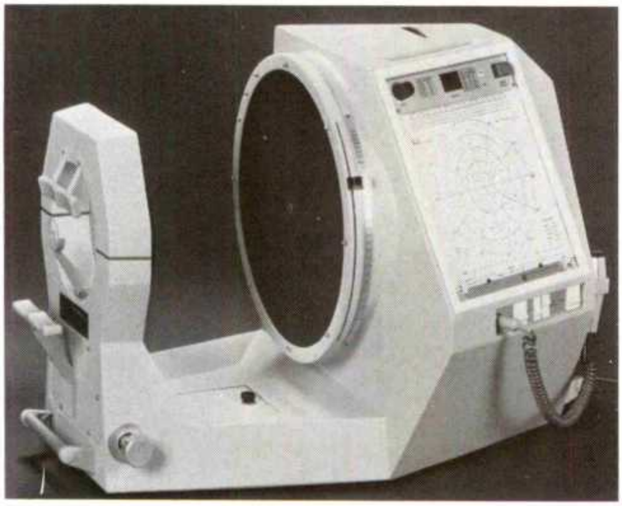

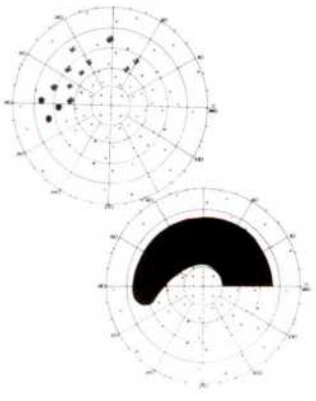

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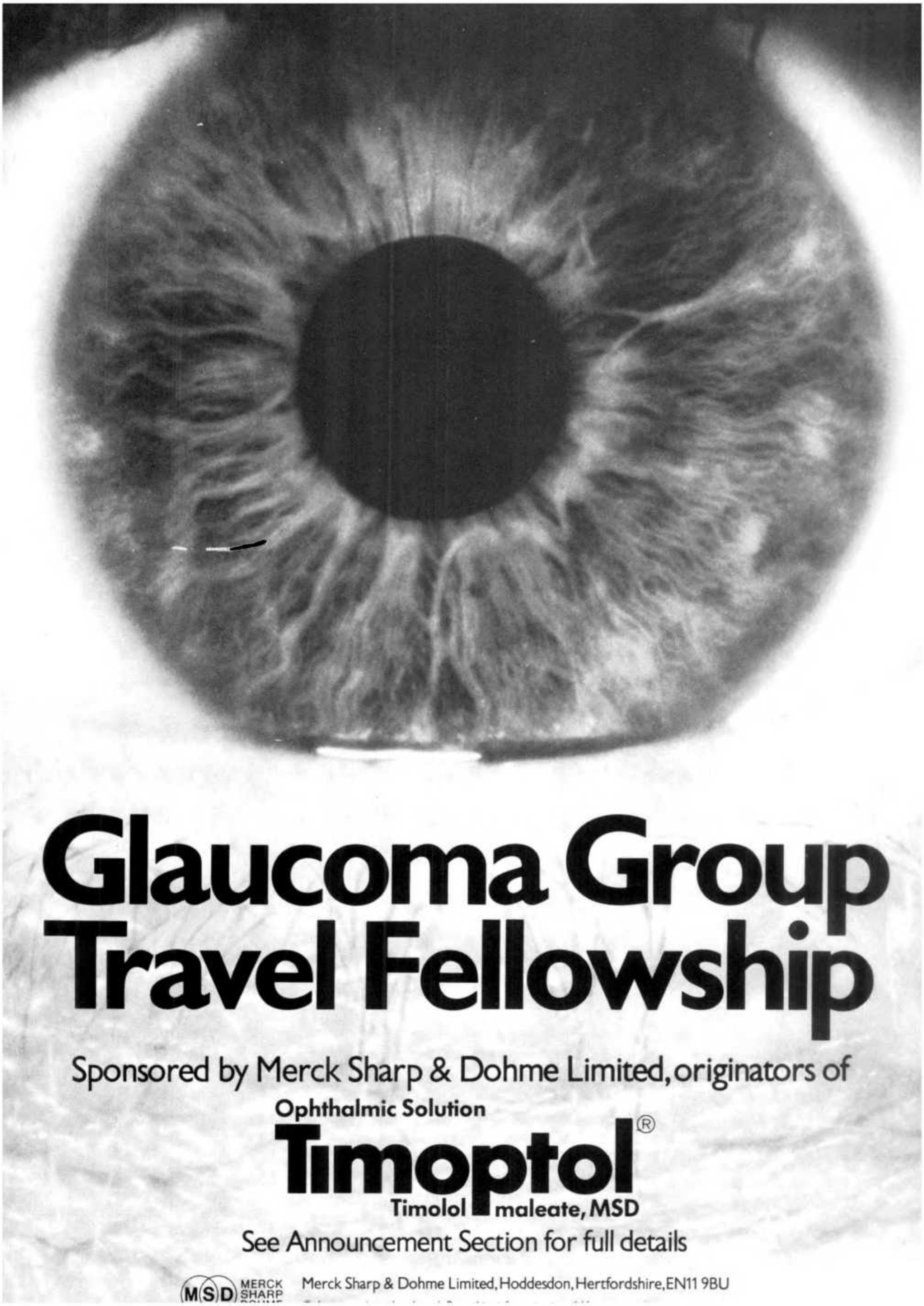

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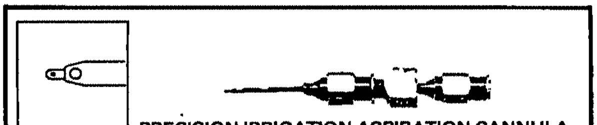
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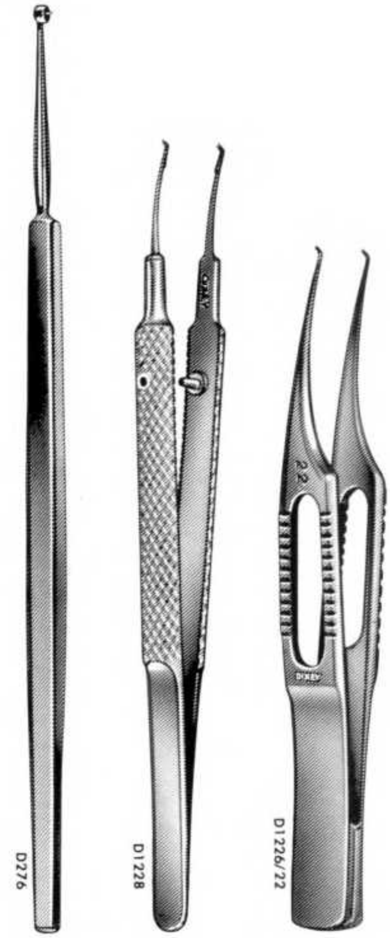

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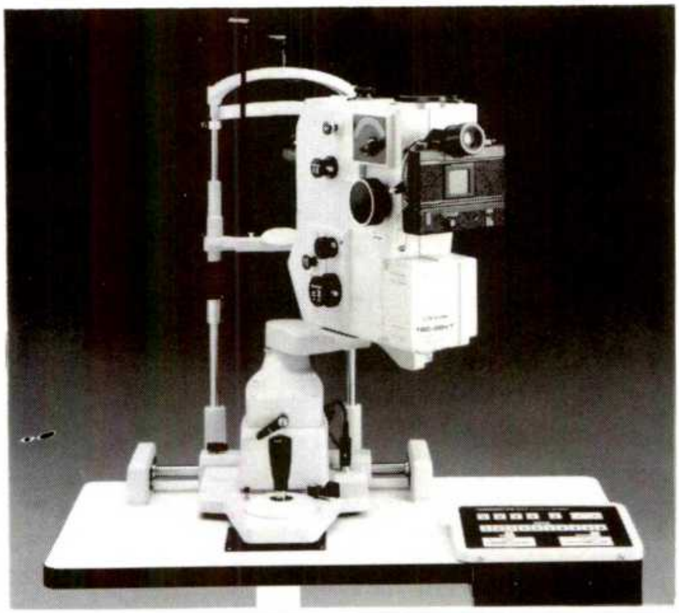

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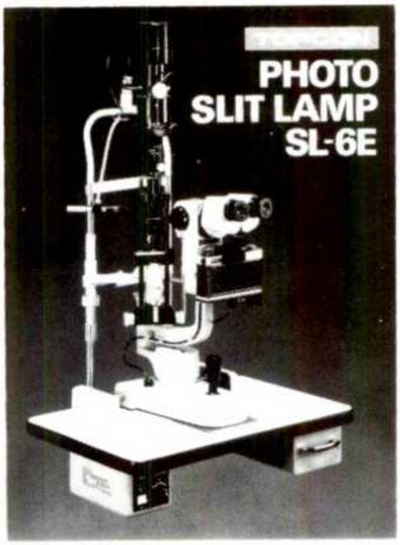

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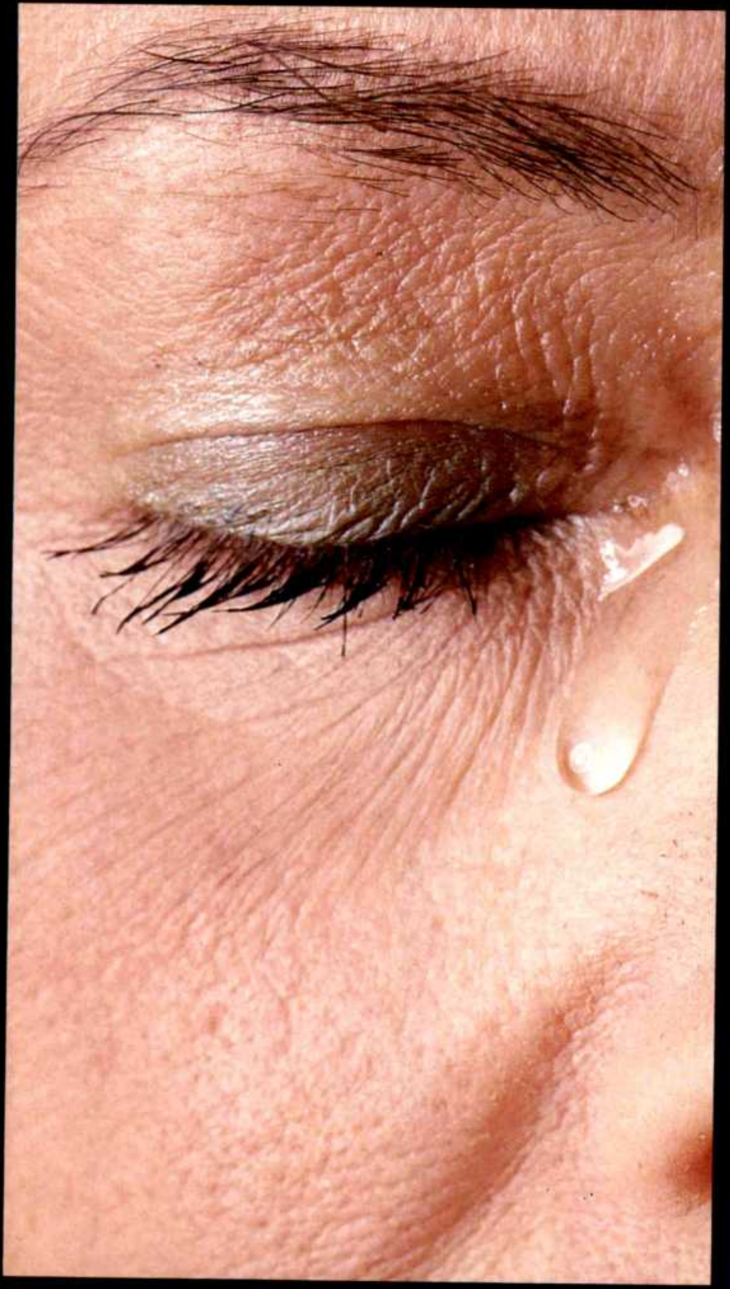

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British Journal of Ophthalmology, 1987, **71**, 325

Editorial: Postmeasles blindness

In Africa measles is a major cause of corneal blindness, which is known as postmeasles blindness (PMB). Various surveys indicate that measles is responsible for 14 to 81% of childhood blindness. In a prospective study of measles in a Kenyan mission hospital keratitis was observed in most children with measles (76%).[1] In most cases this keratitis healed without treatment and without sequelae. However, a small proportion of children (<5%) later developed corneal complications consisting of large corneal erosions or exposure ulcers, leading to secondary infection, corneal ulcers, and perforation. In another study herpes simplex virus was isolated from almost half and measles virus from over 10% of children with active corneal ulcers following measles.[2]

The factors which lead to the development of PMB are not well defined. It has been suggested that malnourishment, particularly vitamin A deficiency, associated immunosuppression, and genetic factors are all involved in the development of PMB. Studies have shown that there did not appear to be any correlation between the extent and severity of measles keratitis and nutritional status.[1] In addition there were no differences in serum prealbumin levels or serum retinol-binding protein levels between malnourished children with corneal ulcers after measles compared with other malnourished children without corneal disease after measles.[2]

The role of immunosuppression in the development of PMB is not clear. PMB is not seen in immunodeficient children with leukaemia in developed countries, who fail to develop a measles rash. While malnourished children may be partially immunosuppressed, they develop immune responses to measles virus during infection. They produce normal levels of antibodies and a severe measles rash, which is the result of cell-mediated immune responses to measles virus. However, these children also shed measles virus for longer, and their sera have inhibitory activity in some in-vitro tests of cell-mediated immunity.[3] It has been suggested that genetic factors contribute to the development of PMB. In African children measles is particularly severe and PMB is common, whereas in Asian children PMB is not common. It may be that African children are particularly susceptible to severe measles and PMB.

The paper by Kogbe and Liotet which appears in this issue describes their studies of tears from children with severe measles. They found that children with measles were deficient in tears. This may suggest that measles virus interferes with normal tear production in some way. This lack of tears must render the eyes of these children particularly vulnerable to secondary infections. They also found that in the early stages of measles children had a normal tear protein pattern or a 'serum' protein pattern due to the transudation of serum proteins through blood capillary walls during acute inflammation. In contrast malnourished children with corneal erosions in the later stages of measles had considerable amounts of transferrin but no other serum proteins in their tears. However, the presence of transferrin in tears was not due to malnourishment, since malnourished children without measles had normal tear protein patterns.

These results raise several important questions. Does measles always cause a marked reduction in tears or are malnourished African children particularly susceptible? Does this deficiency in tear production contribute to the development of PMB? Why do large amounts of transferrin appear in tears, and are the physical properties of tears altered? Does transferrin contribute to the development of PMB, in which case does it appear before, during, or after the development of PMB, or is it a marker of corneal erosions? Measles and PMB can be prevented by vaccination, but until vaccination is universally implemented PMB will continue to cause preventable blindness. In the meantime a better understanding of the factors involved in the development of PMB could lead to the development of cheap, simple, and effective methods of treatment and prevention, which are urgently needed.

M A MONNICKENDAM
S DAROUGAR

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British Journal of Ophthalmology, 1987, 71, 326–330

Tear electrophoretic changes in Nigerian children after measles

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SUMMARY At the laboratory of the National Centre of Ophthalmology, Paris, tear electrophoresis on cellulose acetate support was studied in 56 Nigerian children—32 during and shortly after measles infection and 24 healthy controls. The controls had a normal pattern, while those with measles had patterns consistent with inflammation, most severe in the first week but showing varying degrees of recovery by the third week. Four weeks after measles all cases suffering from malnutrition had patterns with an additional peak. This was shown on further investigation by electrophoresis on polyacrylamide cellulose gel and immunoelectrophoresis to be due to serum transferrin. The normal protein pattern of tears is shown to be altered during and after measles infection.

Clinical observations and reports from Nigeria,[1-4] Zambia,[5] Uganda,[6] Kenya,[7] and Tanzania[8] confirm that measles is the commonest cause of corneal ulceration and the leading cause of blindness in children in Africa south of the Sahara. It would appear to be responsible for much of the 200 000 annual cases of blindness attributed to xerophthalmia in this region. Measles, which can be very severe in African children, is frequently associated with a rapidly progressive corneal ulceration (up to 1% in Nigeria[3]) and protein calorie malnutrition. This is because most of the children are affected by measles between the ages of 1 and 2 years, which corresponds to their weaning period, when they go off the breast before they can take an adult diet.[9] During the attack of measles protracted high fevers, severe anorexia, and frequent oral candidiasis worsen the nutritional status of the affected children.

The pathogenesis of this corneal ulceration following measles remains obscure. Its similarity to keratomalacia led to the estimation of serum retinol-binding protein levels. The results have not been significantly decreased in malnourished children with or without measles to support the theory that the condition may be primarily a manifestation of vitamin A deficiency.

Moreover, administering vitamin A, although effecting an appreciable rise in the concentration of both serum retinol and retinol-binding protein,[10] does not, combined with topical antibiotics, accelerate healing of the corneal ulceration, unlike keratomalacia with secondary bacterial infection. Measles[11] and malnutrition[12] have separately been observed to cause a state of severe depression in cellular immunity. So it was proposed that the severe corneal ulceration is due to an abnormally severe secondary herpes simplex infection,[13] calling for a trial of antiviral agents combined with forms of immunotherapy such as interferon or levamisole.

Recent work on the functions of the tear fluid on the cornea in keratitis sicca syndrome suggested the possibility that the lacrimal gland (an epithelial tissue derivative) might be affected by the measles virus.

We investigated the tears produced by children during the course of measles infection by studying the composition and levels of tear proteins.

Materials and methods

SUBJECTS

In August 1984 and in January 1985 samples of tears were collected from children presenting at the paediatric unit of Ahmadu Bello University Hospital in Zaria and Kaduna, University College Hospital, Ibadan, State Hospital, Ikeja, and Health Centre Tundunwada, Jos. The date of onset of measles, and

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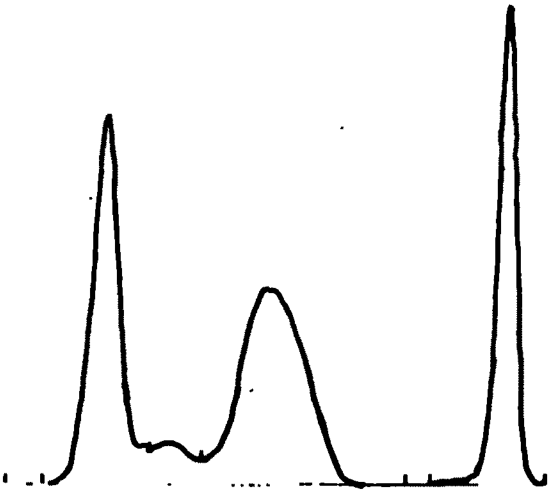

Fig. 1 *Control: normal pattern.*

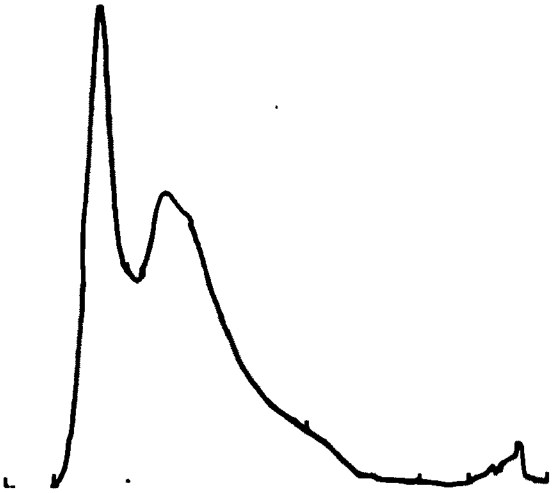

Fig. 3 *Measles week 2: type 2 pattern.*

its ocular and systemic complications, were recorded. Fifty-six children were seen: 32 had measles, while 24 with no history or clinical evidence of measles served as controls matched for age. The ages of the children ranged between 6 months and 3 years.

METHODS

Samples of tear fluid were collected by capillarity with a sterile pointed-ground pipette, between 9 am and 12 noon to minimise evaporation, formol vapour being used as a stimulant for lacrimation. The specimens were centrifuged and the supernatant stored at 4°C until electrophoresis was performed on cellulose acetate support in glycine tris-buffer solution. The strip was stained by Ponceau red, decolorised, and cleared. Further differentiation and identification of proteins was done by carrying out electrophoresis on the polyacrylamide cellulose gel of fresh aliquots of tear samples from cases showing an abnormal change; so also was immunoelectrophoresis of whole serum, diluted serum, and tears in the presence of whole human antiserum on agarose.

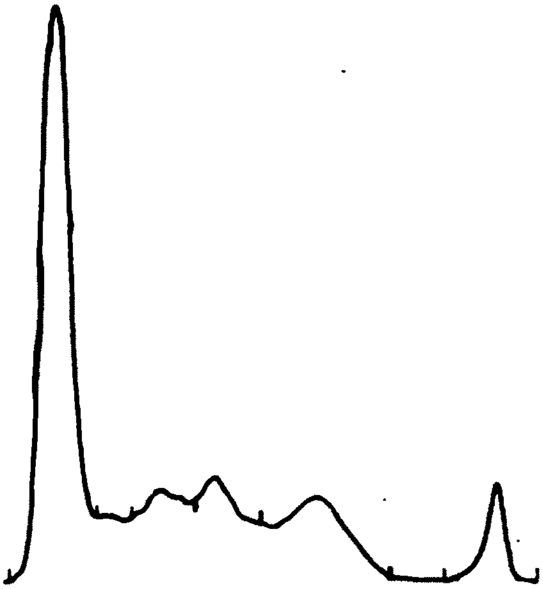

Fig. 2 *Measles week 1: serum-like pattern.*

Results

The number of children suffering from measles was surprisingly small, as there had been a successful measles vaccination campaign the year before. Many paediatric units had to be visited to collect tear samples from 56 children. It was generally observed that the controls produced tears much more readily than those suffering from measles.

ELECTROPHORESIS

All 23 controls had white eyes with no clinical evidence of conjunctivitis. Electrophoresis of their tears showed a splitting into four main bands (Fig. 1). All 19 cases seen during the first week of measles infection had mild to severe conjunctivitis; three had a normal pattern of tear proteins and 16 had patterns similar to that of serum.

During the second week of measles the number of cases seen was much less, as the majority had recovered, and only those with complications reported to the hospital. All seven had mild conjunctivitis. The pattern of tear electrophoresis was still largely similar to that of serum (Fig. 2) in five out of the seven cases, but showed a type 2 pattern (Fig. 3)

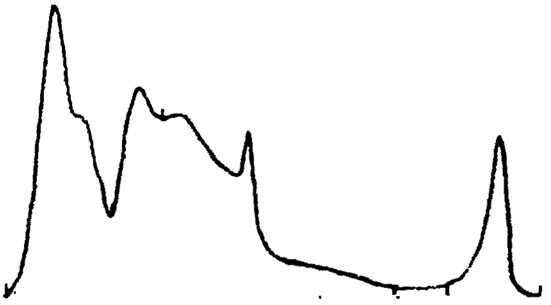

Fig. 4 *Abnormal peak.*

abnormality first described by Liotet *et al.*[14] One of them had in addition an abnormal peak in the middle band (Fig. 4), indicating an appearance of a new protein.

The only patient whose tears were collected in the third week had recovered from measles. He had no clinical conjunctivitis, and showed a normal pattern of tear electrophoresis. The others seen were too ill and had dry eyes as they just cried noisily without shedding any tears.

All five cases seen at four weeks after measles were on treatment for secondary infections and varying degrees of malnutrition. They had no clinical conjunctivitis but had various corneal erosions. In all five the tear electrophoretic patterns were abnormal, as an additional narrow band with a pointed peak showed up on an otherwise normal pattern in two cases (Fig. 5) and on a serum-like pattern in three cases (Fig. 6).

Whereas five of six malnourished children without a history of measles or corneal disease had patterns similar to the controls', one child who had healing bilateral corneal ulcerations following meningitis also had an additional band similar to that seen in cases four weeks after measles.

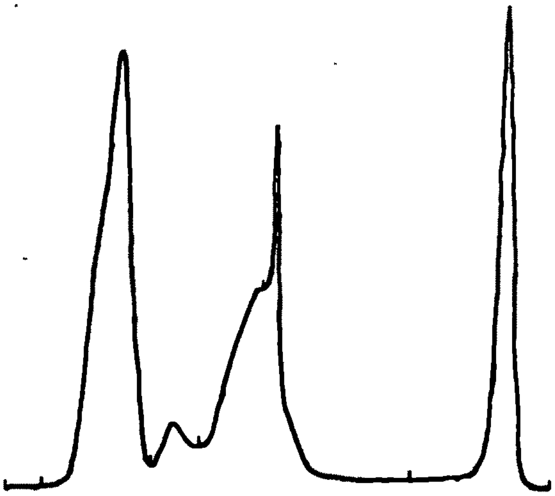

Fig. 5 *Abnormal peak.*

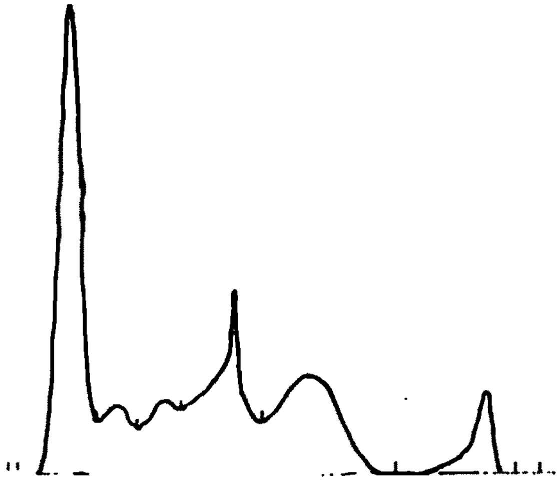

Fig. 6 *Abnormal peak.*

All the tears showing this additional band were examined by electrophoresis on the gel of polyacrylamide cellulose (Fig. 7) and by immunoelectrophoresis (Fig. 8). A prominent band was observed in the position of serum transferrin. We could not determine its quantity as we did not have the specific monovalent antiserum.

Discussion

The observed reduced tear production in children suffering from measles is highly suggestive of measles affecting the lacrimal gland function in tear production. Not only is the quantity reduced, the quality also appears to be altered.

On normal tear electrophoresis our results agreed with that of Liotet *et al.*[15] who described four bands seen on electrophoresis of normal tears on cellulose acetate support.

During measles the appearance of an electrophoretic pattern like that of serum (Fig. 2) in the presence and absence of clinical conjunctivitis more than confirms McClellan *et al.*'s experience which led them to say that children with conjunctivitis could be said to be crying serum.[16]

In normal children only a limited amount of serum proteins are found in tears,[17–20] because a closed blood-tear barrier exists. Hence measles must cause a derangement of this barrier, so that serum proteins move freely into tears from the conjunctival vessels and/or from the lacrimal gland. It is remarkable that this derangement can be detected by tear electrophoresis four weeks after the onset of measles when,

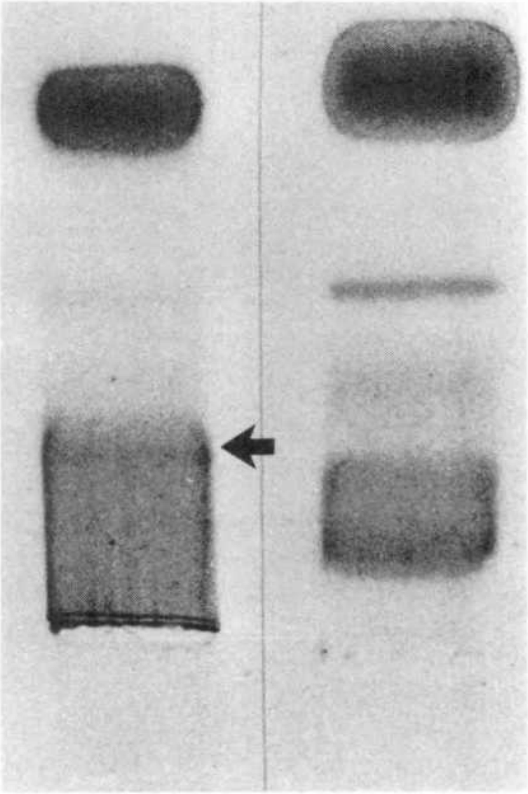

Fig. 7 *Serum transferrin band (arrowed).*

clinically, recovery from conjunctivitis appears to have taken place. This can either mean that the blood-tear barrier remains open for a while or that the lacrimal gland has not yet recovered. Either way, tear electrophoresis is a simple, non-invasive means of assessing lacrimal gland function and conjunctivitis.

The appearance of serum transferrin in electrophoresis of tears from all children with measles complicated by malnutrition and corneal erosion could be another index of derangement caused by measles. Malnutrition per se cannot be incriminated, as all those affected only by malnutrition had normal patterns. The fact that this derangement was likewise seen in a patient who had not measles but meningitis with malnutrition and healed bilateral corneal ulcerations suggests that the derangement may be the cause or the effect of the corneal lesions. The quantity of serum transferrin is too large (from the peak) to be likely to be due to filtration. So we propose two hypotheses:

(1) The first is local synthesis, which is unlikely, because the usual site of synthesis is in the liver, though this should be considered in view of the reports of synthesis at other sites.[21 22]

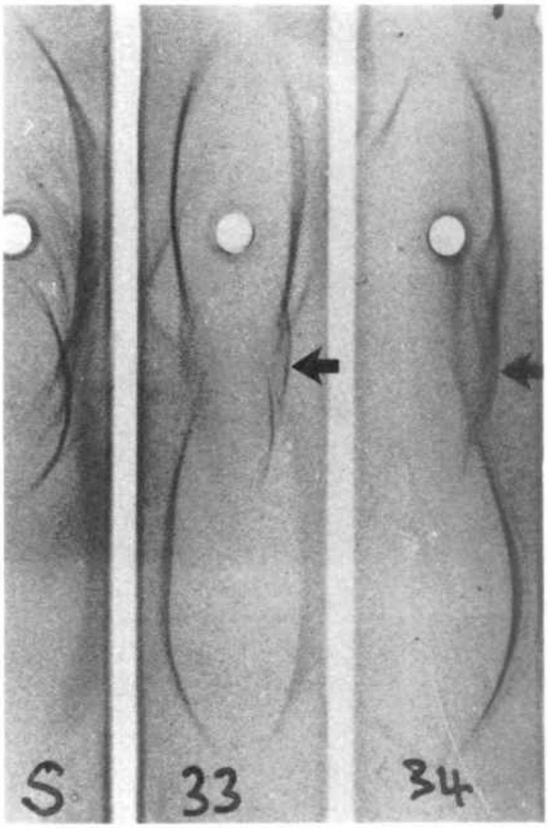

Fig. 8 *Serum transferrin band (arrowed).*

(2) More likely, there could be an active transport from the vascular sector into the tears. The factor for this is yet unknown, although such observations have been made on the cerebrospinal fluid,[23] vitreous, and aqueous humour.[24] This active transportation of serum transferrin will be a source of loss to the body and may partly explain the finding of low values in malnourished Nigerian children reported by Dossetor *et al.*[25]

This could explain another means by which measles renders children malnourished. It will be interesting to find out if the same abnormality occurs in liquid secretions and filtrations such as saliva, cerebrospinal fluid, and aqueous humour after measles.

The ready help and co-operation of the staff of the laboratory of the hospital des Quinze-Vingts and the paediatric clinics in Nigeria are acknowledged with thanks.

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Corneal ulceration, measles, and childhood blindness in Tanzania

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SUMMARY One hundred and thirty Tanzanian children with corneal ulceration were clinically examined to determine the cause of the ulceration. 37% of the ulcers were associated with recent measles infection and 38% of the children had bilateral ulceration. Herpes simplex virus infection was the commonest cause of ulceration in the series, but vitamin A deficiency was the major cause of bilateral ulceration, subsequent blindness, and mortality in this series. Other significant causes of childhood corneal ulceration were the use of traditional eye medicines, confluent measles keratitis, and ophthalmia neonatorum. We discuss the various mechanisms by which measles causes corneal ulceration, and the priorities in prevention and management of corneal ulceration in African children.

Xerophthalmia, a term used to describe the ocular findings caused by vitamin A deficiency, remains one of the six commonest blinding diseases in the world today and the commonest cause of blindness in children.[1,2]

The problem of childhood blindness due to xerophthalmia has been well established in Indonesia[3] and other parts of Asia.[4-7] In Africa, however, although 70% of blind school children are blind from corneal scarring,[8-10] there is still uncertainty over the relative importance and interaction of factors such as measles infection,[11] vitamin A deficiency,[12-18] herpes simplex keratitis,[10,19] and the use of traditional eye medicines[8,20-22] in causing childhood ulceration and corneal blindness.

To investigate this problem we carried out a hospital based study with the aim of identifying by clinical means: (1) the major causes of corneal ulceration in Tanzanian children, (2) the mechanisms by which measles may lead to corneal ulceration, and (3) the major pathways leading to blindness from corneal scarring in children.

Patients and methods

One of us (AF) examined 130 children aged 4 days to 10 years presenting with corneal ulceration to the eye department of Mvumi Hospital in Central Tanzania between October 1981 and June 1985.

All the children were admitted to hospital and basic demographic and historical information documented on a standard form. This included name, age, sex, village of residence, date ulcer first noted, history of measles, use of traditional eye medicines, recent diet, and history of night blindness. Ocular examination with a handlight, lid speculum, fluorescein, and, in co-operative children, slit-lamp microscopy was performed, and photographs were taken of the corneal ulcers. Nutritional status was determined by comparing their weight for age against the Harvard standards. The child was considered normal (well nourished) if his weight for age was greater than 80% of standard, underweight if 60–80% of standard, and marasmic if less than 60% weight for age.

For this special investigation serum samples were drawn for chemical analysis on 41 consecutive cases of the 130 cases in this report. They were also obtained from three controls for each of the children with a diagnosis of measles-associated xerophthalmic corneal ulceration, matched on age, sex, and the presence of measles. The serum was kept frozen until shipment to Baltimore, where it was analysed by high-performance liquid chromatography (HPLC). These values were not used in arriving at the clinical diagnosis.

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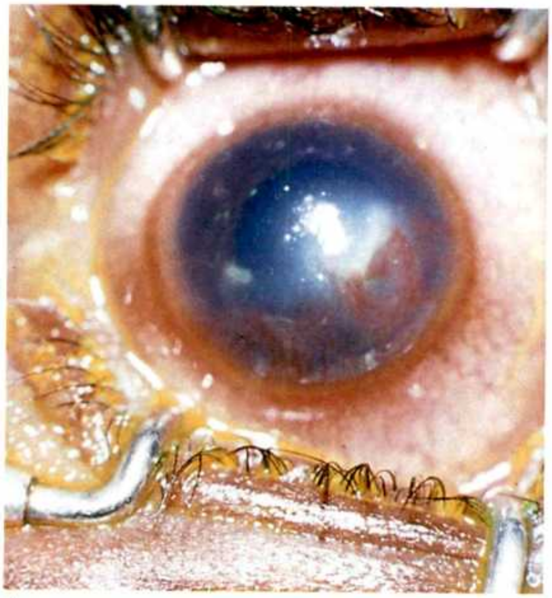

Fig. 1 *Case 1. Right eye of a 2-year-old-girl, showing an irregular corneal ulcer with severe corneal vascularisation.*

From the history and morphological appearance of the ulcer[2,23,24] a provisional diagnosis was made. Specific treatment was then initiated according to the following protocol:

Diagnosis	*Treatment*
Herpes simplex	Idoxuridine 0·1% drops hourly or 0·5% ointment, 5 times daily.
Xerophthalmia	Vitamin A 200 000 IU oral stat, repeat after 1 day and 1 week.
Bacterial ulcer	Chloramphenicol 1% drops hourly, with or without 20 mg subconjunctival gentamicin.
Trachoma	Tetracycline 1% ointment 3 times a day.
Ophthalmia neonatorum	Chloramphenicol 1% drops hourly, with tetracycline 1% ointment 3 times a day.
Exposure keratopathy	Tetracycline 1% ointment stat with eye pad for 1 day.
Traditional eye medicines	Chloramphenicol 1% drops hourly, with hydrocortisone 1% drops 3 times a day after 48 hours.

The child continued to receive a normal diet from the mother unless there was evidence of severe undernutrition, in which case additional food was given in the form of dried skimmed milk, eggs, and oil. Children with diarrhoea received oral rehydration therapy and children with respiratory infections received systemic antibiotics, usually procaine penicillin. Preparations containing multivitamins were not given.

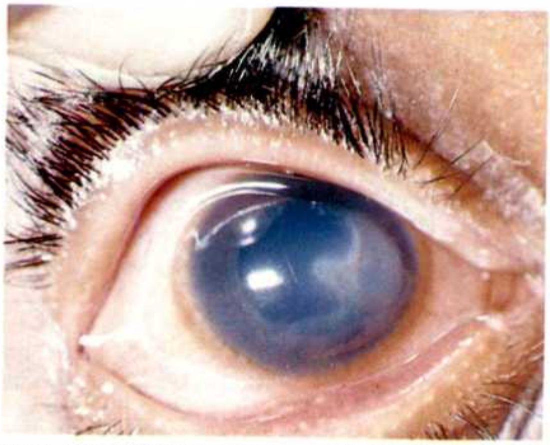

Fig. 2 *Case 1. Right eye of a 2-year-old girl following nine days' treatment with IDU. The ulcer has healed, leaving a superficial corneal scar.*

After 24, 48, and 72 hours the child was re-examined, and, depending on response to therapy and clinical appearance of the ulcer, the management was continued or modified according to the protocol. At discharge a final diagnosis of the aetiology of the corneal ulcer was made based on the history, the clinical appearance of the ulcer, and the response to specific therapy under supervision, as shown in the following case presentations.

Case reports

CASE 1

A 2-year-old girl was admitted with a painful red right eye of at least two weeks' duration. There was no history of measles infection, but she had received chloramphenicol drops for one week to her right eye. On examination she was well nourished, with a normal left eye. The right eye showed an irregularly shaped linear ulcer in the inferonasal quadrant with surrounding stromal oedema and marked vascularisation. There were also several small areas of superficial staining temporally. There was no perforation (Fig. 1). She was treated with 0·5% idoxuridine (IDU) ointment five times a day and gradually improved. Treatment was stopped after nine days, leaving a residual partial-thickness, nasally situated corneal scar (Fig. 2). Three days later a small area of staining recurred which was successfully treated with a further five days' course of IDU.

Diagnosis. Herpes simplex ulceration of the right cornea.

CASE 2

A 20-month-old boy was admitted on 14 April 1984 with a three-week history of measles. There was no history of night blindness, and the mother denied using traditional eye medicines. On examination he was marasmic. The right eye showed limbus-to-

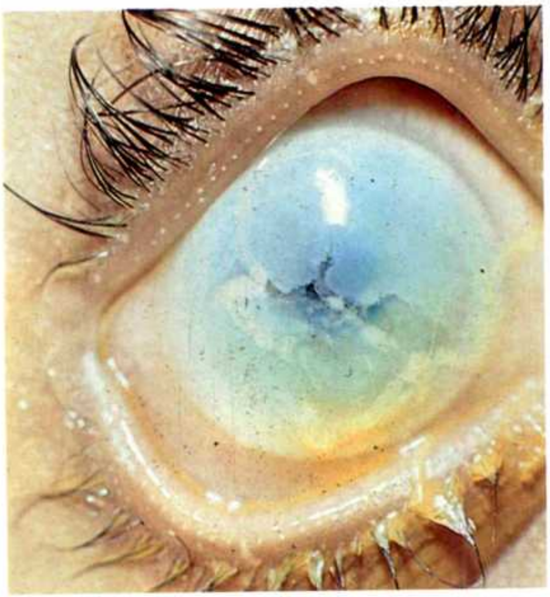

Fig. 3 *Case 2. Right eye of a 20-month-old boy with measles and marasmus. There is limbus to limbus corneal necrosis with a central corneal perforation.*

limbus corneal necrosis with perforation of the central cornea (Fig. 3). The left eye showed sloughing of the cornea with prolapse of iris and vitreous (Fig. 4). The child was treated with oral vitamin A, frequent calorie-protein rich meals, and systemic antibiotics. He died 10 days after admission of pneumonia, at which time the right eye was developing a staphyloma and the left eye was phthsical. Serum vitamin was 40 µg/l (normal 200 µg/l or above), and serum albumin 29 g/l (normal 40 g/l).

Diagnosis. Postmeasles marasmus, with bilateral corneal ulceration due to vitamin A deficiency.

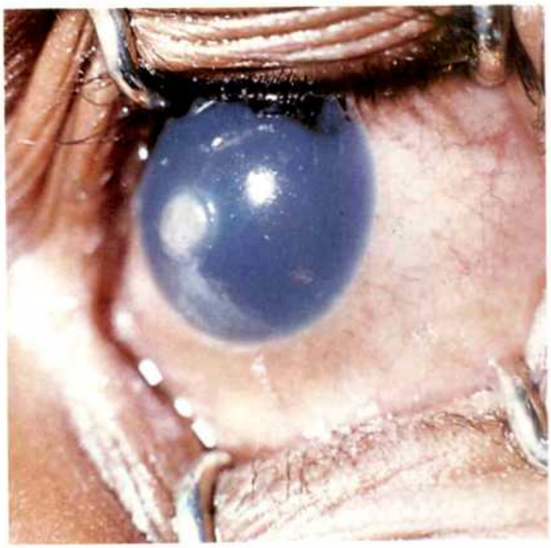

Fig. 5 *Case 3. Left eye of an 18-month-old boy showing corneal xerosis and localised areas of stromal necrosis.*

CASE 3

An 18-month-old boy was admitted on 24 October

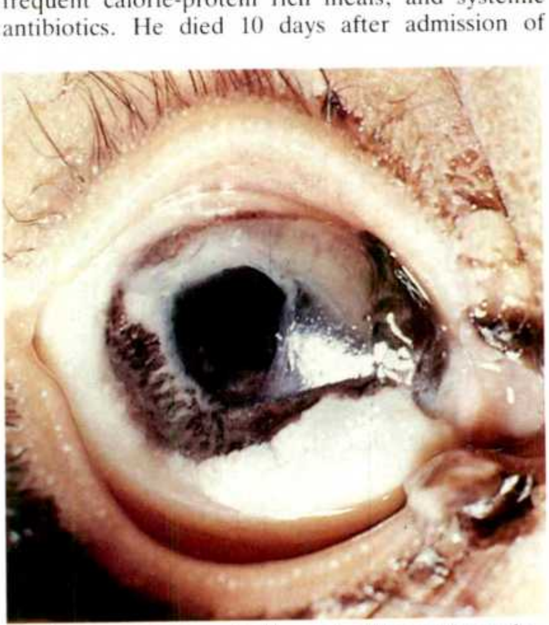

Fig. 4 *Case 2. Left eye of a 20-month-old boy with measles and marasmus. There is complete sloughing of the cornea with prolapse of iris and vitreous.*

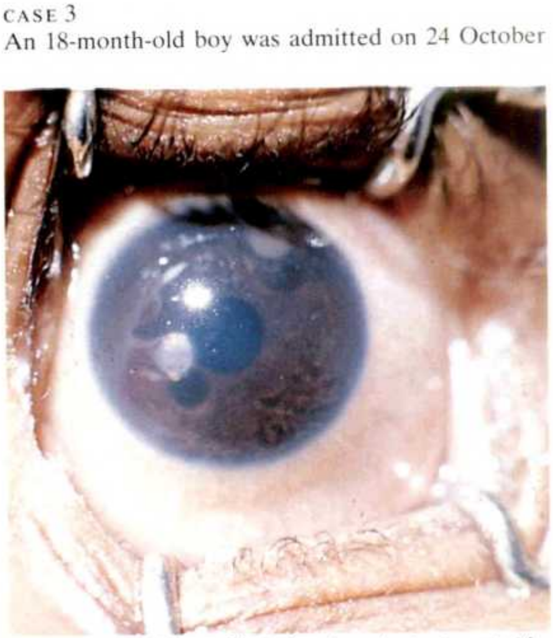

Fig. 6 *Case 3. Same as Fig. 5, five days after treatment with vitamin A. The cornea is now clear, and the areas of stomal necrosis have healed with scar formation.*

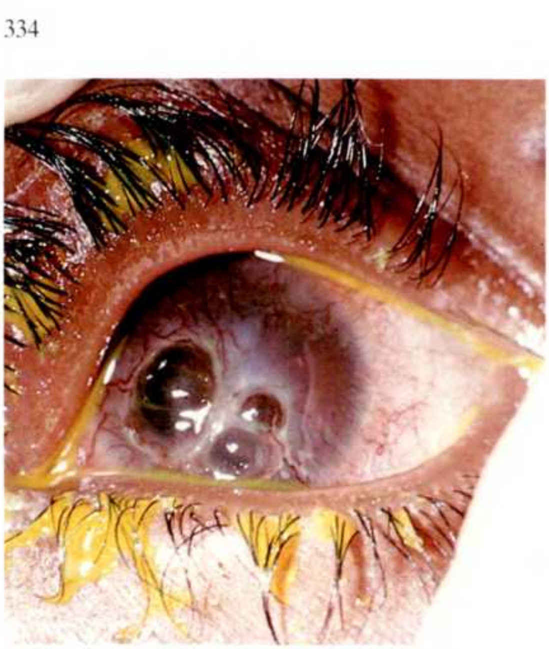

Fig. 7 *Case 4. Right eye of a 10-year-old girl after application of traditional eye medicines. There are three areas of descematocoele formation with marked corneal vascularisation.*

1984. He had suffered from measles six months previously and was underweight. On examination there was bilateral xerosis of the conjunctiva and cornea. In the left eye there were small circular areas of stromal necrosis in the nasal and upper temporal areas of the cornea (Fig. 5). He was given standard vitamin A therapy, with improvement after 48 hours and healing with scar formation after five days (Fig. 6). Serum vitamin A was 20 μg/l (normal above 200 μg/l), and serum albumin 28 g/l (normal 40 g/l).

Diagnosis. Corneal ulceration due to vitamin A deficiency.

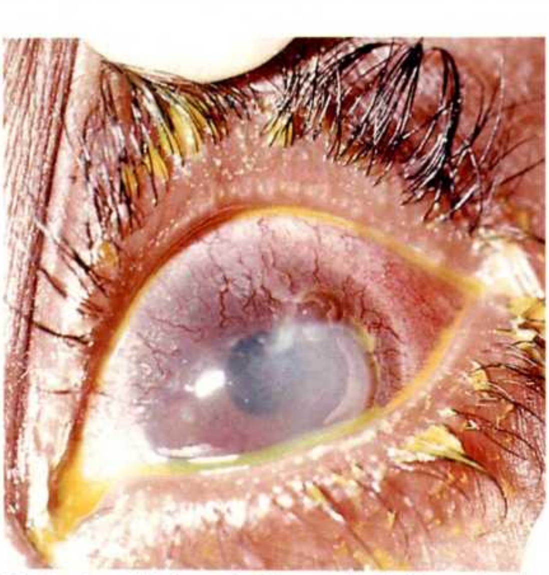

Fig. 8 *Case 4. Left eye of a 10-year-old girl after application of traditional eye medicines. There is one area of descematocoele formation with corneal vascularisation.*

CASE 4

A 10-year-old girl was admitted with bilateral painful red eyes following the use of traditional eye medicines. There was no history of measles and the patient was well nourished. The mother had paid for the traditional doctor to apply 'boiled green herbs' to the girl's eyes because her eyes were red and discharging pus. After the use of the traditional eye medicines her eyes became more painful and blind. On examination both eyes were very red with swollen lids. There were three areas of iris prolapse in the right eye (Fig. 7) and a small corneal perforation with iris prolapse in the superotemporal quadrant of the left eye (Fig. 8). The patient was treated with local antibiotics, and later hydrocortisone drops were added. At discharge, 15 days later, the right eye had an adherent central leucoma with projection of light vision only, and the left eye 6/18 vision with a vascularised peripheral adherent leucoma. Serum vitamin A was 300 μg/l (normal above 200 μg/l), and serum albumin 54 g/l (normal 40 g/l).

Diagnosis. Bilateral corneal ulceration due to traditional eye medicines.

CASE 5

A 2-year-old girl was referred from the paediatric ward with a three-day history of measles and a suspected right corneal ulcer. On examination the child was underweight. The left eye showed superficial punctate keratoconjunctivitis typical of measles keratitis, but with areas of confluent corneal staining nasally and temporally in the exposed area of the cornea (Fig. 9). In the right eye there was a central epithelial corneal ulcer with areas of punctate measles keratitis in the periphery (Fig. 10). The child was treated with tetracycline eye ointment to both eyes, and an eye pad was applied to the right eye. Next day there was no staining in the right eye and minimal measles punctate keratitis in the left eye. Thereafter she made an uneventful recovery. It was thought that this epithelial ulcer (abrasion) was probably due to severe 'confluent' measles keratitis possibly associated with exposure, though clinically there was good lid closure at the time of examination.

Diagnosis. Right corneal ulcer due to measles keratitis (plus exposure).

CASES 6 AND 7

Female twins, A and B, aged 11 months were

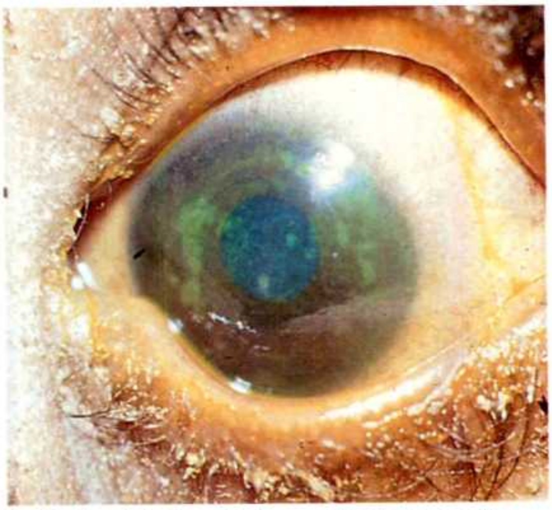

Fig. 9 *Case 5. Left eye of a 2-year-old girl with measles. There are areas of epithelial staining in the mid-nasal and temporal areas, with peripheral punctate keratitis.*

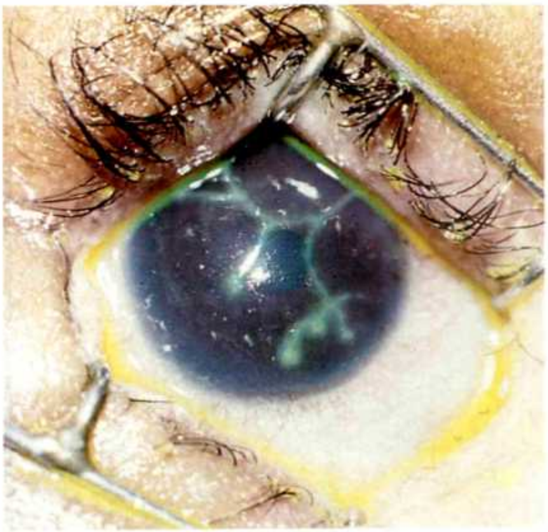

Fig. 11 *Case 6. A dendritic ulcer of the right eye in an 11-month-old marasmic girl (twin A).*

admitted on 9 April 1984. There was no history of measles, but both twins were marasmic. On examination there was a dendritic ulcer in the right eye (Fig. 11), and a geographic ulcer in the left eye of twin A (case 6). Twin B (case 7) had an extensive central geographic ulcer in the right eye and a peripheral geographic ulcer in the left eye (Fig. 12). Both twins were treated with IDU ointment; they were also given oral rehydration solution and systemic antibiotics for gastroenteritis and pneumonia. Twin A's eyes slowly improved over 14 days, so that on 23 April 1984 there was minimal scarring in the right eye and a small area of residual staining with superficial scarring in the left eye. Twin B improved rapidly initially, and within four days of starting IDU there was minimal staining in both eyes. However, despite continued treatment with IDU the herpetic ulcers recurred, especially in her right eye. Twin B died of pneumonia on 23 April 1984, and twin A died 24 hours later of pneumonia and gastroenteritis.

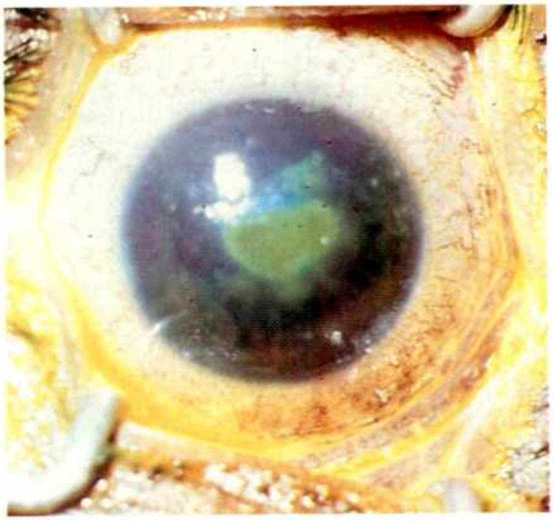

Fig. 10 *Case 5. Right eye of a 2-year-old girl with measles. There is a central epithelial ulcer, with a few areas of punctate keratitis in the periphery.*

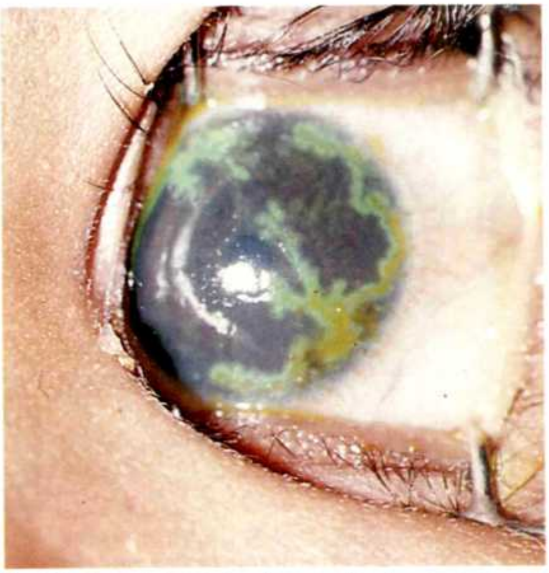

Fig. 12 *Case 7. A peripheral geographic ulcer (twin B).*

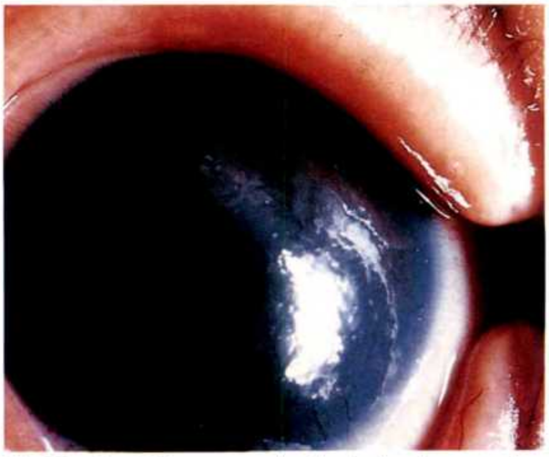

Fig. 13 *Case 8. Twenty-month-old twin showing corneal xerosis two weeks after measles (twin C).*

Diagnosis. Bilateral corneal ulceration in twins due to herpes simplex virus. The cause of death was pneumonia and gastroenteritis (? due to herpes simplex) with marasmus.

CASES 8 AND 9

Female twins aged 20 months were first seen on 22 February 1984. Twin C (case 8) was admitted on the paediatric ward, recovering from measles infection which had started two weeks previously. On examination she was underweight with small ulcers on her lips, face, ear, and scalp typical of herpes simplex. She also had bilateral conjunctival and corneal xerosis, but no frank corneal ulceration (Fig. 13). She was given vitamin A therapy according to the protocol, and within 48 hours both corneas were clear. Thereafter she made an uneventful recovery.

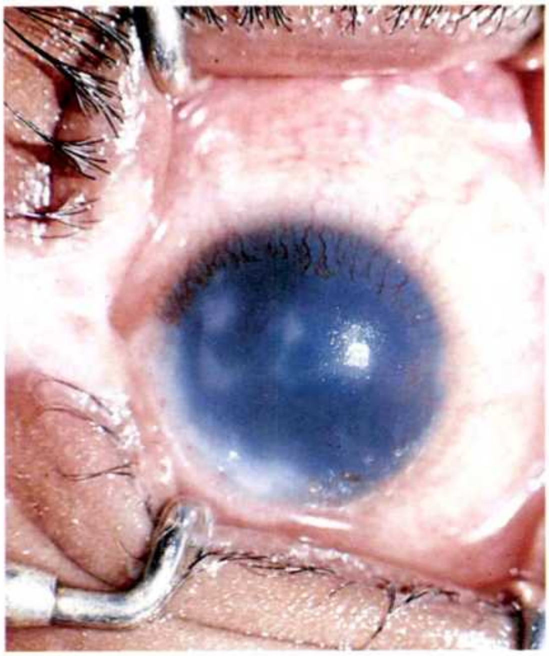

Fig. 14 *Case 9. Twin D showing an ulcer of the inferior temporal limbal area of the right eye, with extension into a central dendritic ulcer.*

On the same day twin D (case 9) developed fever and red eyes. On examination she was underweight, with Koplik's spots and bilateral superficial punctate keratoconjunctivitis. A diagnosis of measles was made and she was given 200 000 IU of vitamin A as a prophylactic against developing xerophthalmia like her twin sister. Six days later she was seen again with a watering red right eye. The left eye was normal but the right eye showed a branching ulcer in the inferotemporal quadrant of the cornea and ulceration of the lateral canthus (Fig. 14). She was treated with IDU drops and gradually improved over six days (Fig. 15). Treatment was stopped on 6 March 1984 and both twins discharged home. It seems likely that twin D was infected with measles and possibly also herpes simplex virus by twin C.

Diagnosis. Twin C had measles associated xerophthalmia (corneal xerosis), with cutaneous herpes simplex. Twin D had measles associated with herpes simplex ulceration of the right cornea.

In many rural areas of the developing world, such as Mvumi Hospital, rapid and accurate microbiological and biochemical investigations are not available and cannot be relied upon in the diagnosis and management of corneal ulceration. It is therefore necessary to place great emphasis on the history and a careful examination of the morphological appearance of the corneal ulcer in deciding its most likely cause. Vitamin A estimations were performed on 41 of 130 children in this series to see if the clinical diagnosis was accurate (Fig. 16), but the results were not available until the clinical study was over.

Children with superficial punctate keratitis due to measles were not included in this study unless they developed definite corneal ulceration, such as in cases 5 and 9.

Results

Of the 130 children under 11 years of age with corneal ulceration 63 (48%) were male and 67 (52%) female. The distribution by age was remarkably similar for the different aetiological groups. Overall 47% of cases were under 2 years of age and 76% under 5 (Table 1).

Our clinical diagnoses were nearly always supported by serum vitamin A levels obtained prior to treatment (Fig. 16). The occasional discrepancy

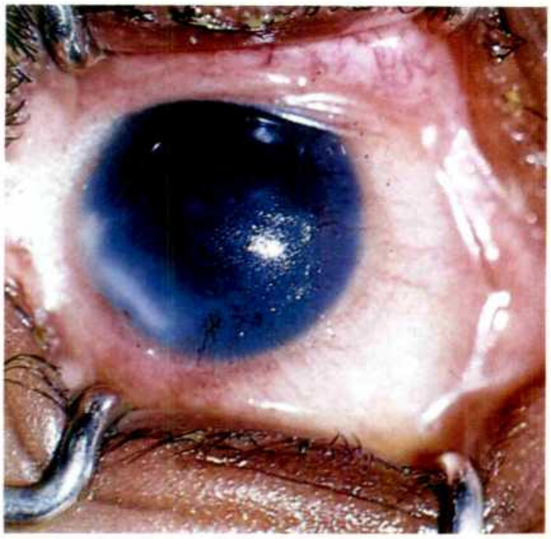

Fig. 15 *Case 9. Same as Fig. 14, six days after starting IDU treatment.*

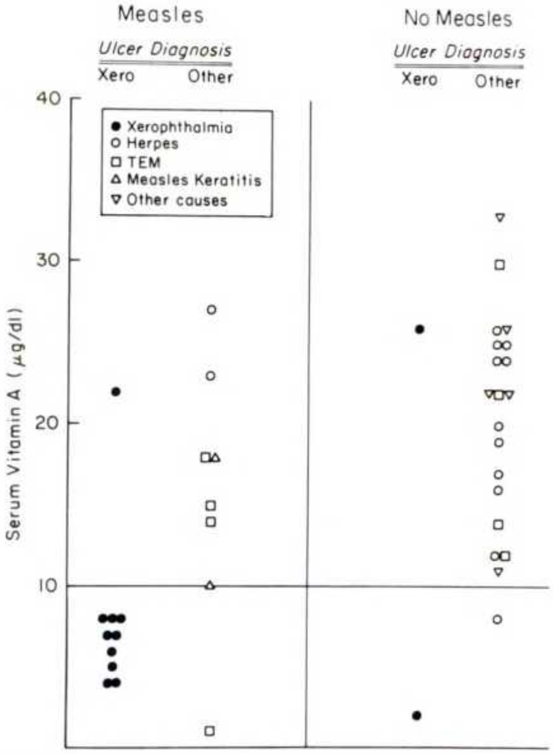

Fig. 16 *Serum vitamin A levels on 40 consecutive children with corneal ulcers. One additional child, with clinical diagnosis of xerophthalmia, received vitamin A before serum was obtained. Diagnosis established on clinical grounds as described in 'Methods', before serum vitamin A levels were available. (SI conversion: μg/dl × 10 = μg/l).*

Table 1 *Aetiology of corneal ulceration by age in 130 Tanzanian children*

Cause	*No.*	*<2 years* %	*2–4 years* %	*5–10 years* %
Vitamin A deficiency	34	47	35	18
Herpes Simplex	47	51	21	28
Traditional Eye Med	18	44	28	28
Other known causes	21	57	19	24
Measles confluent keratitis	5	20	60	20
Unknown	5	0	80	20
Total	130	47	29	24

illustrates the potential complexity and multifactorial nature of corneal ulceration in this group of children. Of the two children with a clinical diagnosis of xerophthalmia, but normal vitamin A, the one with measles had bilateral perforating ulcers and the one without measles a unilateral ulcer that seemed to respond to vitamin A. In retrospect both cases may have been caused by the use of traditional eye medicines. One case of measles associated with corneal ulceration not diagnosed as xerophthalmia had extremely low serum levels of vitamin A and retinal binding protein. The patient had initially been diagnosed as vitamin A deficiency with evidence or traditional medicine in the lower fornix. As he did not respond to vitamin A the final clinical diagnosis was changed to traditional eye medicine. Obviously there is no reason why the child could not have had both. Mean serum vitamin A on the eight xerophthalmic children with measles was 68 μg/l and for their 24 matched controls 102 μg/l ($p<0\cdot01$).

The single commonest cause of corneal ulceration was infection with herpes simplex virus (HSV) accounting for over one-third of all cases. Vitamin A deficiency (xerophthalmia) was responsible for a quarter of the ulcers, and the use of traditional eye medicines (TEM) for nearly 14%. Other causes included bacterial ulceration (10 cases), trauma (three), ophthalmia neonatorum (three), trachoma (three), and exposure ulceration of the cornea (two) due to proptosis from orbital swellings. In 10 children

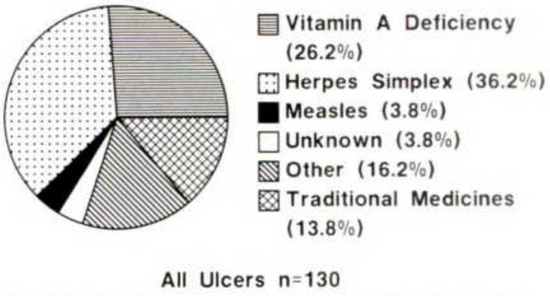

Fig. 17 *Aetiology of corneal ulceration in 130 Tanzanian children with corneal ulcers.*

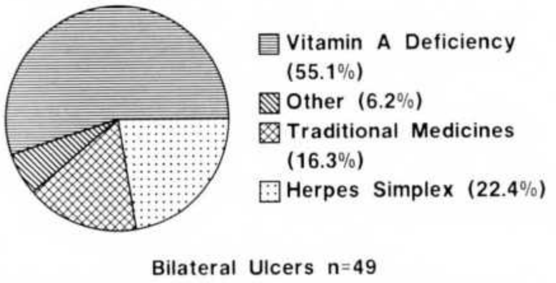

Fig. 18 *Aetiology of corneal ulceration in 49 Tanzanian children with bilateral corneal ulcers.*

no definite cause could be given. Two of these 10 children absconded before response to therapy could be assessed, a further three had nondescript superficial erosions unrelated to measles, and the remaining five had areas of epithelial ulceration within 10 days of measles infection, as demonstrated by case 5, which were attributed to measles 'confluent' keratitis (Fig. 17).

In 38% of children the corneal ulceration was bilateral. Vitamin A deficiency was responsible for over a half of the bilateral cases, and herpes simplex for nearly a quarter. The remaining 11 cases were due to the use of TEM (eight cases) and ophthalmia neonatorum (three cases) (Fig. 18).

There was a history of measles infection within one month before developing corneal ulceration in 37% of the 130 children and in 57% (28 of 49) of those with bilateral ulceration. Vitamin A deficiency was responsible for half of the measles-associated corneal ulcers, herpes simplex for one-fifth, and TEM for nearly 17%. Five of the 48 children with measles-related ulceration showed superficial central corneal staining, which was thought to be caused by either a severe 'confluent form' of measles keratitis or exposure keratopathy (Fig. 19). One child with a perforated corneal ulcer one month after measles and a history of using TEM absconded before the effects of therapy could be seen.

Recent measles infection was associated with nearly three-quarters of corneal ulcers caused by vitamin A deficiency, almost a half of those due to TEM, and one-fifth of ulcers caused by herpes simplex (Table 2). Measles infection was associated with 29% of corneal ulcers in under 2-year-olds, 70% in 2–4-year-olds, and 37% in 5–10-year-old children. 92% of xerophthalmic ulcers and all TEM ulcers in children 2 to 4 years old were associated with measles.

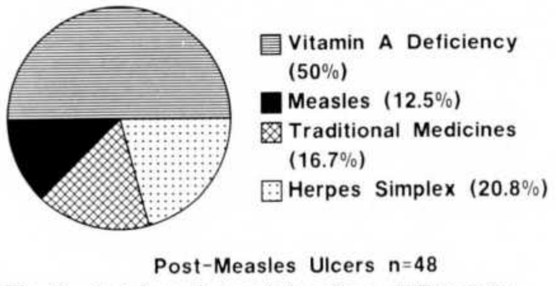

Fig. 19 *Aetiology of corneal ulceration in 48 Tanzanian children with measles-associated corneal ulceration.*

Table 2 *Corneal ulceration within one month of measles infection, by cause and age as a percentage of all ulcers, in Tanzanian children*

Age	*Xerophthalmia*			*Herpes simplex*			*TEM*		
	N	*n*	%	*N*	*n*	%	*N*	*n*	%
<2 yrs	16	10	62	24	3	12	8	1	12
2–4 yrs	12	11	92	10	3	30	5	5	100
5–10 yrs	6	3	50	13	4	31	5	2	20
Total	34	24	71	47	10	21	18	8	44

N=total number of children seen with corneal ulceration due to specific cause. n=number of children seen with corneal ulceration due to specific cause which developed within one month of measles infection.

The longer the duration between onset of measles and presentation, the more likely the ulceration was due to vitamin A deficiency. 63% of ulcers occurring within seven days of measles onset were due to causes other than vitamin A deficiency, while 56% of cases occurring two weeks or later after measles were due to vitamin A deficiency. 70% of measles-associated herpes simplex ulcers occurred within 14 days of the onset of measles rash.

Over half (11 of 20) of the unilateral cases of postmeasles corneal ulcers involved the corneal stroma, while 82% (23 of 28) of the bilateral cases showed involvement of the stroma in at least one eye, and seven children showed total bilateral corneal necrosis (Table 3).

Table 3 *Clinical appearance of active corneal ulceration occurring within one month of measles infection in 48 Tanzanian children*

Type of ulcer	*Unilateral*		*Bilateral*	
	n	%	*n*	%
Epithelial:				
dendritic ulcer	1	2	0	0
geographic ulcer	3	6	3	6
central abrasion	5	10	0	0
xerosis with stain	0	0	2 (1)	4
Stromal:				
non-perforated ulcer	8	17	6 (1)	13
perforated ulcer	3	6	10	21
total corneal necrosis	0	0	7 (4)	15
Total	20	41	28 (6)	59

( )=Number of children who died.

Table 4 *Clinical appearance of active corneal ulceration due to vitamin A deficiency in 34 Tanzanian children*

Type of ulcer	*Non-measles*		*Measles*		*Total*	
	Uni.	*Bi.*	*Uni.*	*Bi.*	*N*	*%*
Corneal xerosis	0	0	0	2 (1)	2	6·0
Non-perforated round, oval ulcers	3	1	3	6 (1)	13	38·2
Perforated round, oval ulcers	0	3 (2)	1	5	9	26·4
Total corneal necrosis	0	3 (2)	0	7 (4)	10	29·4
Totals	3 8·8%	7 (4) 20·6%	4 11·8%	20 (6) 58·8%	34	100·0

( )=Number of children who died. Uni.=unilateral. Bi.=bilateral.

Six children with corneal ulceration following measles died (12·5%), of which all had bilateral ulceration and four had total bilateral corneal necrosis.

The clinical appearance of the ulcers caused by vitamin A deficiency and herpes simplex is given in Tables 4 and 5. Bilateral involvement of measles-associated ulcers was seen in 83% (20 of 24) of cases due to vitamin A deficiency, but only 30% (three of 10) of the ulcers due to herpes simplex infection. A geographic type of corneal ulcer was the commonest pattern of herpetic ulceration, occurring in 51% (24 of 47) of cases, with a dendritic pattern being seen in only 25% (12 of 47) (Table 5).

The overall mortality in hospital was 10·8%, but nearly one in three of the children with corneal ulcers due to vitamin A deficiency died despite hospital admission and management (Table 6). Sixteen children (six of whom died) were judged to have bilateral corneal lesions which would result in blindness (binocular vision of less than 3/60), of which 11 (69%) were due to vitamin A deficiency and three (19%) to the use of TEM.

Corneal ulceration induced by vitamin A deficiency usually occurred after measles (76% of cases), was bilateral in 79%, and was associated with high mortality (29%) and blindness (32%). In contrast herpetic corneal ulceration followed measles in only 21% of cases, was bilateral in only 23% of cases, and was associated with significantly lower mortality (6%) and blindness (2%) (Table 6).

Table 5 *Clinical appearance of active corneal ulceration due to herpes simplex virus in 47 Tanzanian children*

Type of ulcer	*Non-measles*		*Measles*		*Total*	
	Uni.	*Bi.*	*Uni.*	*Bi.*	*N*	*%*
Dendritic	8	3	1 (1)	0	12	25·5
Geographic	14	4 (2)	3	2	24	51·1
Atypical limbal	5	0	3	0	8	17·0
Deep stromal	2	1	0	0	3	6·4
Totals	29 61·7%	8 (2) 17·0%	7 (1) 14·9%	3 6·4%	47	100·0

( )=Number of children who died. Uni.=unilateral. Bi.=bilateral.

Table 6 *Characteristics of the different causes of corneal ulceration in Tanzanian children*

Cause	*No.*	*Bilateral*		*Measles associated*		*Blind**		*Mortality*	
		n	*%*	*n*	*%*	*n*	*%*	*n*	*%*
Vitamin A deficiency	34	27	79	24	76	11	32	10	29
Herpes simplex	47	11	23	10	21	1	2	3	6
Traditional eye medicines	18	8	44	8	44	3	17	1	5
Other known causes	21	3	14	0	0	1	5	0	0
Measles confluent keratitis	5	0	0	5	100	0	0	0	0
Unknown	5	0	0	1	20	0	0	0	0
Totals	130	49	37·7	48	36·9	16	12·3	14	10·8

*Blind=binocular vision less than 3/60.

Discussion

MEASLES-ASSOCIATED CORNEAL ULCERATION

Measles infection is usually accompanied by lacrimation, photophobia, and a keratoconjunctivitis which lasts for two to 10 days. Trantas[25] and Dekkers[11] have reported a superficial punctate keratitis due to measles virus which usually resolves as the skin rash fades, leaving no permanent sequelae. However, serious corneal complications following measles were documented in Europe in the last century and early part of this century,[26 27] but apart from very rare reports,[28] blindness following measles-associated corneal ulceration has now disappeared from Europe.

In Africa, however, 1 to 4% of hospitalised children with acute measles develop true corneal ulceration as distinct from punctate keratitis.[11 19 29–31] In this series 25% of unilateral and 57% of bilateral corneal ulcers occurred within one month of previous measles infection—findings similar to studies elsewhere.[3 32] The ulceration was bilateral in 58% (28 of 48) of children developing corneal ulcers after measles, and 11 of these 28 children with bilateral measles-associated corneal ulcers were considered to have ulceration which would result in blindness despite hospital treatment. Measles was responsible for 69% of all children examined and judged to go blind from corneal scarring in this hospital based series. This figure is in general agreement with results from surveys carried out in blind schools in other African countries (33–79%),[8 14 18 33] confirming the importance of measles as a predisposing factor for corneal ulceration and blindness in African children.

The mechanism by which measles causes corneal ulceration in Africa is controversial and complex. Herpes simplex corneal ulceration has been reported after measles.[11 18 19 34] We deemed 21% of measles-associated ulcers to be herpetic in origin, of which 30% (3 of 10) were bilateral. The ulceration was usually epithelial and occurred within two weeks of the measles rash in 80% of cases. There was no case of measles-associated herpetic ulceration which resulted in blindness, though superficial corneal scarring was a common sequela.

The use of TEM was responsible for 17% of measles-associated ulcers and for nearly one-fifth of the bilateral ulcers which resulted in children going blind. It seems probable that measles conjunctivitis causing red eyes, together with a local knowledge that measles and red eyes result in blindness, leads mothers to use TEM in an effort to help the child with measles.[35 36] It is possible that the children in whom TEM were used already had an underlying eye disease due to vitamin A deficiency or herpes simplex virus, but clinically these ulcers did not show the typical appearances of xerophthalmia or herpetic ulceration, nor did they respond to specific therapy.

Vitamin A deficiency was the commonest cause of measles associated ulceration (50%) and of subsequent bilateral blindness. Early signs of xerophthalmia—night blindness and Bitot's spots—were uncommon, occurring in only five of 24 children with measles-associated ulcers due to vitamin A deficiency. Sommer[3 37 38] suggests that this absence of early clinical signs of vitamin A deficiency in measles may be due to the accompanying inflammation which causes the conjunctival xerosis and Bitot's spots to disappear, or possibly measles causes a sudden decompensation in vitamin A metabolism in children who are asymptomatic but have depleted stores of vitamin A in the liver. The reduced dietary intake,[39] malabsorption,[40] and increased demands[41] for protein and vitamin A which occur in measles may result in a sudden fall in available vitamin A to the tissues and consequent corneal ulceration. The evidence for vitamin A deficiency being the cause of these ulcers was based on the clinical appearance of the ulcer (Table 3) and the dramatic response to therapy (as in case 3). Vitamin A biochemistry was available on 41 of the 130 children, and was in agreement with the clinical diagnosis in the great majority of cases (Fig. 16). Measles is known to have a depressive effect on vitamin A levels.[3] However, there was a statistical difference in vitamin A levels between the children with measles-associated, clinically diagnosed, xerophthalmic ulcers, and age/sex measles matched controls without ulcers.

Of children with measles-associated corneal ulcers 11% developed a round, epithelial, usually central ulcer, which occurred within 10 days of the measles rash appearing. In some children this ulceration was seen to develop from the more typical measles superficial punctate keratitis (case 5). These epithelial ulcers healed quickly when treated with antibiotics and patching of the eye. This type of ulcer is probably due to a confluent form of measles keratitis accentuated by desiccation of the cornea due to exposure. Dekker described this appearance in 4% of children with typical measles SPK, and demonstrated the presence of measles virus in corneal scrapings.[11] Our experience suggests that this type of measles-associated epithelial corneal ulceration has a good prognosis and does not usually lead to severe ulceration and blindness.

We therefore suggest that there are four main pathways by which measles may cause corneal ulceration: (1) sudden decompensation of subclinical vitamin A deficiency; (2) the use of traditional eye medicines; (3) infection with herpes simplex virus; (4) confluent measles keratitis with or without exposure.

Ulceration due to vitamin A deficiency or TEM often results in bilateral severe corneal destruction with a high rate of blindness. It may be very difficult clinically to know how much of the ulceration is due to the vitamin A deficiency and how much has been caused by TEM, and both causes may be significant factors in the same individual. Confluent measles keratitis or secondary infection with herpes simplex virus is more likely to be unilateral and usually involves only the epithelium and anterior corneal stroma, with complete healing or superficial corneal scarring being the usual outcome.

The relative importance of each individual cause of measles-associated ulceration in different parts of Africa will depend on (1) the prevalence of vitamin A deficiency and undernutrition in the childhood population, (2) local practices in relation to measles infection—for example, the use of TEM, or the withholding of food and water[35]—and (3) the prevalence of herpes simplex virus infection in children and their mothers. These factors will vary in time and place according to the availability of food and seasonal variations in infectious diseases.

HERPES SIMPLEX

Corneal ulceration due to HSV has been previously documented from African countries.[11 18 19 42] In this study 36% of all childhood ulcers and 45% (37 of 82) of non-measles ulcers were herpetic in origin.

It has been suggested that children with malnutrition or measles are more susceptible to herpes simplex infection because of suppression in cell-mediated immunity.[42–44] This may explain some of the corneal ulcers seen in this series in severely under-nourished children (cases 6 and 7) and measles (case 9). However, ulceration did occur in apparently well nourished children in the absence of measles. In this group it was often noted that the child was suffering or recovering from malaria, and that childhood admissions with herpetic ulceration peaked each year during the malaria season. One possible explanation is that the fever associated with malaria (or measles) may cause shedding of the HSV[45] and subsequent herpetic keratitis.

51% of the herpetic ulcers showed a geographic or amoeboid pattern, 23% were bilateral, and 51% occurred in children under the age of 2 years. All these characteristics are atypical for 'Western' herpetic ulceration and are usually associated with herpetic infection in patients with depressed cell-mediated immunity. Herpes simplex virus may cause pneumonitis[46] and disseminated infection[44] leading to death. Three out of 47 children (6·4%) with herpetic ulcers died in this series. One child died during the first week of measles infection, and the other two were severely malnourished twins (cases 6 and 7), who may have died of disseminated herpetic disease.

Children with herpetic corneal ulceration were intensively treated with idoxuridine ointment or drops, and the ulceration usually healed in seven to 14 days, leaving residual superficial scarring and vascularisation. Two children returned with a recurrence in the same eye and one child with a new herpetic ulcer in the other eye during the study period. Only one child was judged to become blind in both eyes due to herpetic infection, though most were left with superficial corneal scarring, a reduction in visual acuity, and the possibility of recurrent disease later in life.[47]

It would appear that HSV is a common cause of corneal ulceration in children, being associated with measles, malaria, and malnutrition, but because of its unusual and late presentation it may often go undiagnosed. It may occasionally be associated with disseminated herpes infection and death. Blindness is, however, uncommon, though some visual loss from corneal scarring and recurrent disease in later life seem likely.

VITAMIN A DEFICIENCY

Vitamin A deficiency was found to be the most important cause of bilateral ulceration (27 of 49), measles-associated ulceration (24 of 48), and resultant bilateral blindness (11 of 16). The clinical appearances varied from small, punched out, round or oval ulcers involving the corneal stroma to complete necrosis of the cornea. The more severe the corneal lesion the more likely it was to be bilateral, and the child was more likely to die (Table 4). The response to therapy in early cases is dramatic, with healing of the ulcer and scar formation within four to five days of oral vitamin A administration (case 3). However, in late cases, where there is limbus-to-limbus corneal necrosis, it is impossible to salvage the eye despite vitamin A therapy (case 2). Clinically many of the children with vitamin A deficiency were noted to have dry eyes, dry mouth, a high pitched croupy cough, and to develop respiratory infections. The high mortality (29%) in children with ulceration due to vitamin A deficiency is similar to findings elsewhere.[3]

Because of the high mortality and high rate of blindness associated with vitamin A deficiency, and because treatment is simple and inexpensive, the prevention, early diagnosis, and treatment of vitamin A deficiency must be a priority in any area where protein-energy malnutrition or childhood blindness due to corneal scarring from measles is a problem.

TRADITIONAL EYE MEDICINES

The diagnosis of corneal ulceration due to TEM is based upon a history of using TEM—which the mothers are usually reluctant to confess to—together with the appearances of chemical conjunctivitis and irregular atypical corneal ulcers (case 4). These ulcers do not respond to therapy with vitamin A or antivirals, and usually take three to four weeks to settle on antibiotics, with resultant dense corneal scarring. There is nearly always an underlying eye disease which has caused the mother to use the traditional medicines. This may be measles keratoconjunctivitis, bacterial conjunctivitis, herpes simplex keratitis, xerophthalmia, or any other eye disease. In this series two cases followed the use of TEM in the eye for cutaneous anthrax of the eyelid. It is often difficult to decide whether the TEM or underlying eye disease are most responsible for the corneal ulceration.

Very little is known about the substances used in preparing these medicines, though plants and human or animal urine are often included.[35] The ulceration may be caused by a caustic effect on the cornea from plant extracts, or possibly by secondary infection with bacteria (including *Neisseria gonorrhoeae*) or fungi after the epithelium has been damaged.

Because of the difficulties in obtaining a positive history, and the variety of clinical appearances, the diagnosis of ulceration due to TEM is probably underestimated. The consequences of using TEM may be drastic, with nearly half of the ulcers being bilateral and a significant number resulting in blindness in both eyes.

OTHER CAUSES OF CORNEAL ULCERATION

Other known causes of corneal ulceration in childhood included ophthalmia neonatorum, trauma, bacterial infection, corneal exposure due to proptosis, and trachoma. None of these were related to measles infection, and only those cases due to ophthalmia neonatorum were bilateral, one of which patients became blind. There was no case of fungal keratitis.

CONCLUSION

Many factors are involved and interact in producing corneal ulceration in African children. They include measles infection, the use of traditional eye medicines, herpes simplex infection, and vitamin A deficiency. The frequency of herpetic ulceration in young children has probably been underestimated, in part owing to the atypical clinical presentation. The importance of the use of TEM is likely to vary from one place to another and is difficult to define because of its interaction with other eye diseases.

Measles infection appears to be the major precipitating factor which puts the African child at risk of developing corneal ulceration and becoming blind, while vitamin A deficiency was the most important cause of bilateral ulceration and resultant blindness in this study, and was also associated with a very high mortality.

Measles vaccination programmes and the provision of an adequate intake of vitamin A in the diet of preschool children, though logistically difficult to accomplish, must remain the first priorities in the prevention of childhood blindness in Africa.

The prophylactic use of one vitamin A capsule (200 000 IU) to all children with measles or undernutrition (less than 80% weight for age) would seem to be a reasonable short-term medical intervention, while nutrition education programmes aimed at increasing the dietary vitamin A for preschool children are developed.

The majority of childhood corneal ulcers in many African countries will present initially to a primary health worker or medical auxiliary. In this situation it is recommended that all children with corneal ulcers be given 200 000 IU of vitamin A orally (immediately and 24 hours later) and intensive antibiotics (hourly eye drops or eye ointment at least four times a day). Steroids in any form must not be used, and should not be available to the general medical auxiliary. It is unlikely that antivirals will be available in rural situations, but mechanical debridement of herpetic ulcers in children should be considered only by those experienced and well trained in the diagnosis and management of herpetic keratitis.

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Ischaemic optic neuropathy complicating cardiopulmonary bypass

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SUMMARY Bilateral anterior ischaemic optic neuropathy occurred in two patients undergoing cardiopulmonary bypass grafting. The causes may have been vasoconstriction of the posterior ciliary arteries by increased circulating angiotensin and diminished ciliary blood flow in the setting of systemic hypotension and elevated intraocular pressure.

A small number of visual complications of cardiopulmonary bypass have been described. Visual field disturbance, usually due to transient optic pathway ischaemia, and asymptomatic retinal emboli are the commonest.[1]

Anterior ischaemic optic neuropathy (AION) describes infarction of the optic nerve head, characterised by sudden painless loss of vision initially associated with optic disc oedema, resolving to optic atrophy.[2] Hayreh has shown that the laminar and prelaminar regions of the optic nerve head and the peripapillary choroid are supplied by the posterior ciliary arteries.[3] These arteries are susceptible to obliteration with fall in perfusion pressure, and the optic nerve head is thus vulnerable to infarction. AION is a relatively common cause of acute visual loss in the elderly.[4] It has previously been described in cardiopulmonary bypass patients by Sweeney *et al.*,[5] but it is not listed in reviews of complications of bypass surgery. This paper reports two cases of bilateral AION resulting in severe visual impairment marring otherwise successful coronary artery surgery, and discusses pathogenesis.

Case reports

CASE 1

A 46-year-old man underwent coronary artery bypass graft surgery in which a membrane oxygenator and non-pulsatile perfusion were used for 74 minutes, with hypothermia (28°C). Surgery and anaesthesia were apparently uncomplicated. When the patient regained mental alertness on the second postoperative day he complained of visual disturb-

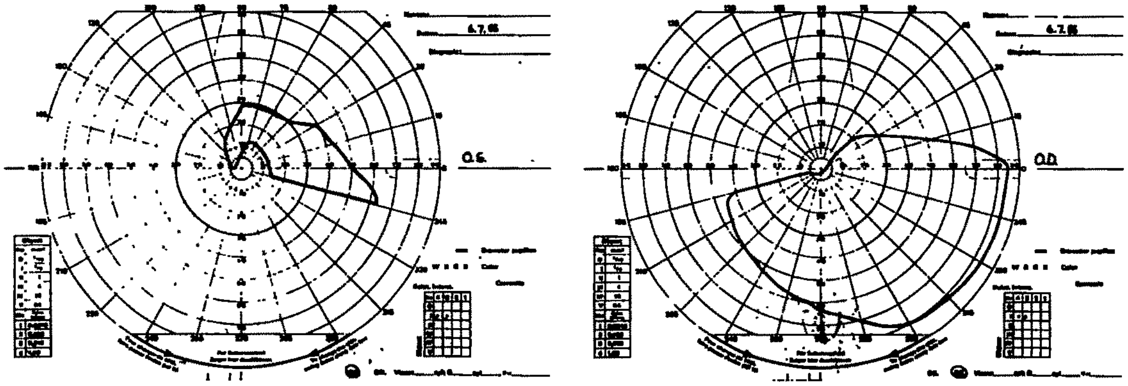

Fig. 1 *Case 1. Left visual field loss inferiorly and superotemporally, leaving a small island of vision. Right superior altitudinal field defect.*

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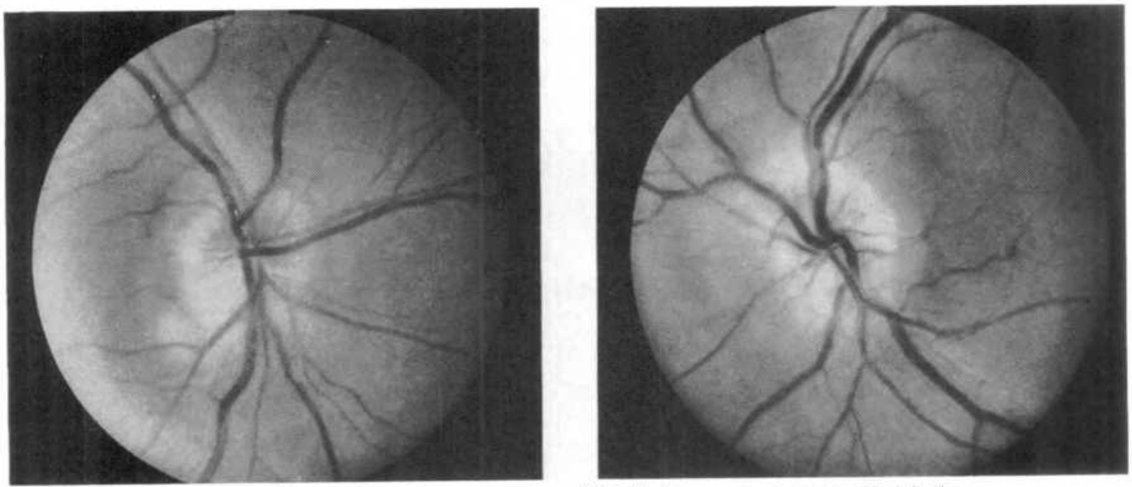

Fig. 2 *Case 1. Optic disc swelling two days after surgery. A small left disc haemorrhage is seen at 2 o'clock.*

ance. On examination visual acuity was reduced in both eyes to counting fingers. Upper and lower altitudinal field defects (Fig. 1) and a left relative afferent pupil defect were noted. The optic discs showed diffuse pallid oedema with a left disc haemorrhage (Fig. 2). Examination was otherwise normal.

Fluorescein angiography showed bilateral optic disc leakage of dye, but no other abnormality of choroidal or retinal circulation. CT brain scan, packed cell volume, serum viscosity, and erythrocyte sedimentation rate were all normal. A diagnosis of AION was made. A course of corticosteroid was prescribed on an empirical basis, but visual acuity and field loss remained at the level noted at first assessment. Within 10 weeks optic atrophy was evident, particularly inferiorly on the right and superiorly on the left (Fig. 3).

CASE 2

A 63-year-old man underwent coronary artery bypass graft surgery in which a membrane oxygenator and non-pulsatile perfusion were used for 90 minutes, with hypothermia (28°C). No complication was apparent until seven days following surgery, when he was examined on account of visual disturbance. Visual acuity was reduced to 3/60 in both eyes; a superior visual field defect was noted in his right and a central scotoma in his left eye (Fig. 4). There was a left relative afferent pupil defect. Optic discs showed

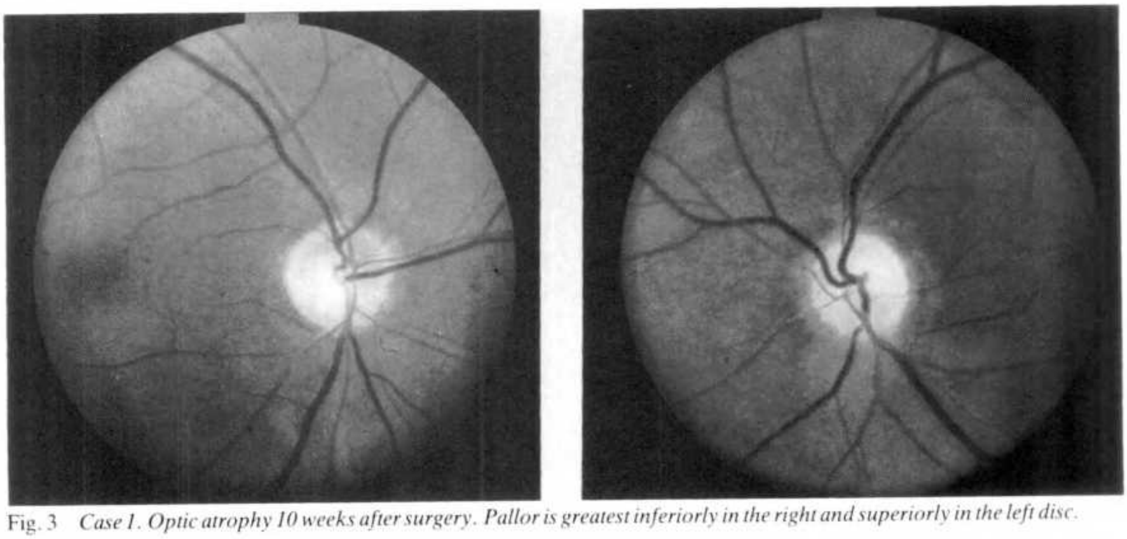

Fig. 3 *Case 1. Optic atrophy 10 weeks after surgery. Pallor is greatest inferiorly in the right and superiorly in the left disc.*

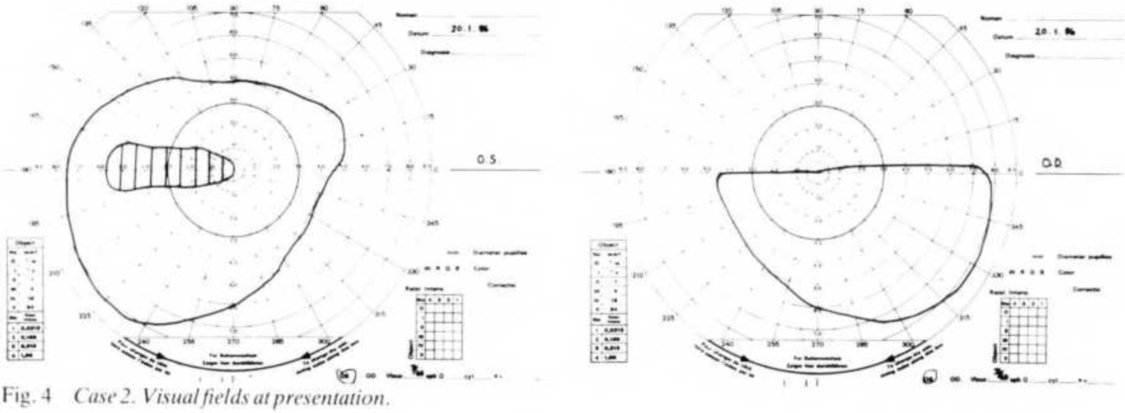

Fig. 4 *Case 2. Visual fields at presentation.*

florid bilateral pallid oedema with haemorrhages at the left disc margin (Fig. 5). He had no other neurological deficit.

Fluorescein angiography showed sectors of disc hypoperfusion and disc leakage of dye (Fig. 6). Investigations were otherwise normal. A diagnosis of AION was made, and no improvement in vision occurred.

Discussion

AION usually affects patients over the age of 50 years. It is an important cause of visual loss in this age group; any recovery of vision is unusual and no treatment has been shown to aid recovery. Hypertension, arterial disease, diabetes mellitus, and giant cell arteritis are commonly associated disorders.[2] Bilateral simultaneous AION is rare, having been reported in cases of acute blood loss,[6] diabetes,[7] giant cell arteritis,[8] and following cardiopulmonary bypass.[5]

The lamina cribrosa and the prelaminar region are the components of the optic nerve involved in AION. The posterior ciliary artery is the only supply to these regions, rendering them vulnerable to infarction. It is known that the posterior ciliary arteries need not be occluded, and emboli are considered rarely to cause AION. The arterial supply to the disc head passes through the surrounding choroid, which is under the influence of the intraocular pressure. As soon as artery perfusion pressure falls below the intraocular pressure, the disc circulation is compromised.[2]

Sweeney *et al.*[5] reported seven cases of AION, of which three had bilateral lesions. Hypotensive episodes due to haemorrhage at surgery occurred in four cases. In addition, these authors considered

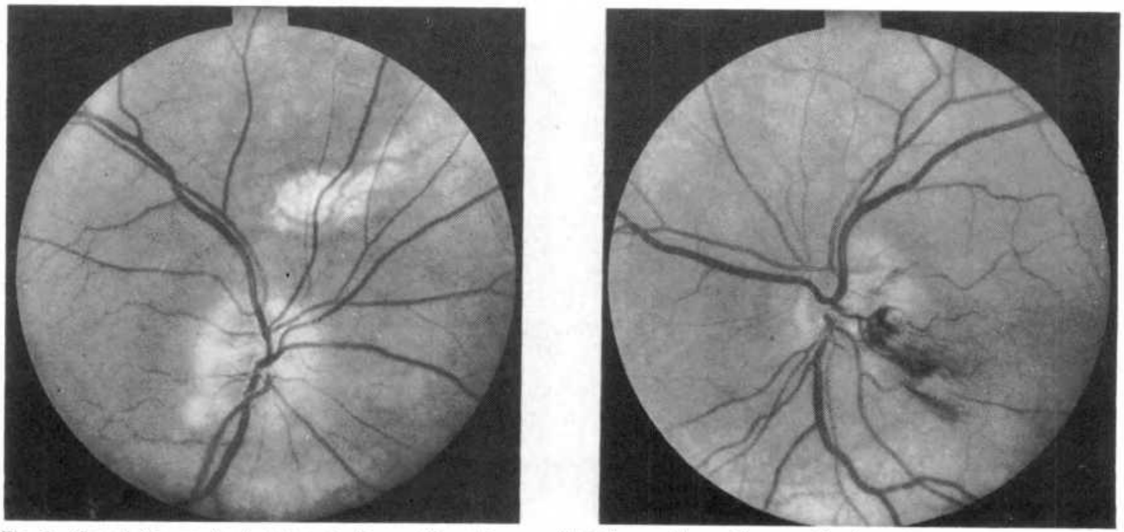

Fig. 5 *Case 2. Generalised right optic disc swelling. Temporal left disc swelling with nerve fibre layer haemorrhage.*

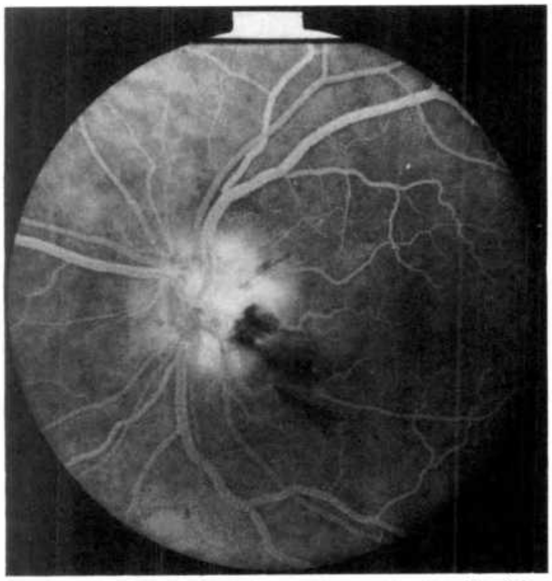

Fig. 6 *Case 2. Late phase fluorescein angiogram of the left disc shows temporal leakage of dye and haemorrhage.*

hypothermia and complement system activation by a bypass bubble type oxygenator as possible causative factors. However, anaesthesia was uncomplicated and minimal blood loss occurred at operation in the cases we report. We propose that systemic hypotension and defective autoregulation of optic nerve blood flow with respect to intraocular pressure during bypass are a more likely cause of AION. Research in our departments has shown that the systemic arterial pressure drops immediately to about 70 mmHg and the intraocular pressure rises briskly on commencement of cardiopulmonary bypass.[9] Furthermore, increased circulating angiotensin could cause optic nerve ischaemia through its powerful vasoconstrictor effect on the ciliary vessels. Angiotensin rises substantially during bypass and particularly with nonpulsatile perfusion.[10] It has been shown to cause defective autoregulation of optic nerve blood flow in response to change in intraocular pressure.[11] The effect of this potent vasoconstrictor might be especially significant in a patient with known arterial disease.

Pressure on the globe might cause a rise in intraocular pressure, but a frame over the patient's face prevents pressure on the globe during the period of unconsciousness.

In conclusion, like other neurological complications of cardiopulmonary bypass, AION may occur in routine, seemingly uncomplicated operations, but, unlike most, it causes devastating long term disability. Clinical evidence of its occurrence may be unnoticed for days. Pathogenesis is uncertain, and no treatment is available. With increasing numbers undergoing coronary artery bypass surgery the need for awareness of AION has prompted this report.

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Is irradiation a justifiable treatment of choroidal melanoma? Analysis of published results

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SUMMARY Analysis of the literature shows that dissemination of choroidal melanomas generally occurs after the 7 mm diameter stage, that doubling times of uveal melanomas vary from 30 to 365 days, and that death from metastases occurs 30–40 doubling times after dissemination. Tumour related death within three years after therapy is caused by pre-existing metastases. Survival rates for less than four years after therapy are therefore irrelevant in evaluating the efficacy of therapeutic regimens. Considerably higher postirradiation than postenucleation death rates after a mean 10-year follow-up period have been reported, and this difference can be explained by (1) a reported mean clinical tumour regression rate of 31% two years after irradiation and (2) histopathological studies which revealed that 42 out of 43 irradiated melanomas contained viable tumour, while only 50% showed necrosis. The doubtful value of preserving vision does not justify the high risk of avoidable death from metastases in irradiated patients.

The purpose of this paper is to present an analysis of the published survival statistics of patients after irradiation of a choroidal melanoma, now that sufficient time has elapsed for the accumulation of reliable data. This analysis has led to the following introductory considerations: (1) almost all survival statistics after enucleation are based on follow-up periods of 10–25 years or until death; (2) almost all survival statistics after irradiation are based on follow-up periods of a few months to no more than three to four years, despite the fact that much more time has elapsed since radiotherapy has been employed; (3) communications on survival statistics after irradiation never mention that a follow-up period of less than four years is irrelevant with regard to the influence of the irradiation on the survival rate.

Time between dissemination and metastatic death

Collins *et al.*[1] stated that death from metastases cannot occur before 35–40 doubling times after dissemination. A doubling time is the necessary time for a primary tumour or a metastatic tumour to double its volume. Rümke *et al.*[2] and Rampen[3] measured the increase in size of skin melanomas and calculated the doubling times: they reached values in the range 20–266 days. Most uveal melanomas are more slowly growing tumours than skin melanomas, and plausible assumptions have been advocated,[4] and accepted,[5] that the doubling times of uveal melanomas range from 30 to 365 days. This implies that the shortest possible interval between dissemination from a uveal melanoma and death from metastases is three years. This interval may extend to more than 30 years. Therefore death from metastases within three years after any form of therapy was started must have been due to metastases which had been present before this therapy. Differences in survival rate, when two forms of therapy are compared might thus, after five years, provide an indication of the effect on survival by these therapies, but 10-year or longer follow-up periods are needed to achieve decisive arguments in favour of a certain therapy.

Gass[6] reported the first calculated doubling times of choroidal melanomas. He found in seven patients with clinically enlarging tumours which necessitated enucleation a wide spectrum of doubling times, which ranged between two and 30 months. In 14 cases of slower growing melanomas which were observed and the eye not enucleated a much larger range of 10–135 months was calculated for the doubling times. Gass assumed that part of the latter group of tumours

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were naevi. He admitted that there are important limitations to the clinical measurement of changes in size and volume of intraocular tumours. These limitations can easily be demonstrated in histopathological slides by the presence of lengthy, non-elevated intrachoroidal extensions of choroidal melanomas.

Most melanomas studied by Gass appeared to grow at a relatively constant rate, consistent with that predicted by Gompertzian curves of exponential growth. Gass stated that his findings did not support the conclusions of Zimmerman and colleagues[7] that enucleation is responsible for deaths from metastases. He emphasised that his findings argue against one of the fundamental assumptions by Zimmerman *et al.*,[7] namely, that all melanomas have a relatively uniform slow growth rate prior to enucleation. According to Gass's figures death from metastases does not occur before 6·6 years after dissemination, because his shortest doubling time was 2 months. It is possible that a shorter calculated doubling time would have been found if a larger series of patients with clinically enlarging tumours had been studied.

Stage at which dissemination starts

We still do not know at which stage a choroidal melanoma develops the capacity to metastasise. This stage can, however, be derived with a high degree of certainty from two American reports[8 9] on the survival rates of patients treated by enucleation for small melanomas in the <7 mm and <10 mm diameter groups. In both series the size had been assessed by histopathological examination. The tumour related death rate of all patients with a melanoma in the <7 mm diameter group was nil, while death rate from metastases of patients with a melanoma <10 mm was 22·7% after 10 years in the first series[8] and 14·3% after 15 years in the second series.[9] The smaller death rate (14%) after 15 years in the second series than after 10 years in the first series (22%) results from a much higher percentage of melanomas <7 mm diameter in the second series. Analysis of these figures reveals that, because the tumour related death rate was nil in both <7 mm diameter groups, all metastatic deaths in the <10 mm diameter groups had occurred in the 7–<10 mm diameter groups. Table 1 shows that the tumour related death rates in these two 7–<10 mm diameter groups were 35·5% and 40·4% respectively, compared with nil in the two <7 mm diameter groups.

One patient with a melanoma <7 mm diameter in the series of Thomas *et al.*[9] had metastases but had not yet died. Only one case of death from metastases after enucleation in a patient with a melanoma <7 mm diameter has been separately reported.[10] It seems reasonable to postulate that, in general, choroidal melanomas are unlikely to shed cell emboli before they have reached the 7 mm diameter stage.

Reported results after radiotherapy

It is relevant at this point to discuss the survival data obtained from patients treated by enucleation and the survival data obtained after treatment by irradiation. Many 10-year or longer follow-up reports on choroidal melanoma patients after enucleation[11] reveal without exception a tumour related death rate of about 50%. Jensen[12] published a 25-year follow-up of 302 patients—with a follow-up percentage of 99·8%—of whom 51% had died from metastases. Thus enucleation of eyes containing a melanoma of any size saves half the patients from tumour related death. This figure of 50% can be improved considerably by enucleating melanoma containing eyes at the earliest stage. We can now detect small melanomas clinically at a much earlier stage than formerly.

It has already been emphasised above that, despite sufficient lapse of time, almost all survival statistics after irradiation are still based on follow-up periods of a few months to no more than three to four years. This holds for the references[13–20] and for the publications not specifically referred to from these same sources. Although some authors[13–16 18 19 21] claim a longer follow-up period than three to four years, their reports do not permit an assessment of survival after these longer periods. All the above mentioned reports are irrelevant in evaluating the effect of radiation treatment on the survival rate, because tumour related death during the first three to four years after treatment is most likely to be caused by metastases present before the therapy was started. A

Table 1 *Follow-up reports on enucleated small choroidal melanomas*

	Davidorf et al.[8] *10 years*			*Thomas* et al.[9] *15 years*		
Diameter	<10 mm	<7 mm	7–10 mm	<10 mm	<7 mm	7–10 mm
Number	50	18	32	65	42	23
Percentage deaths from metastases	22·7%	0%	35·5%[a]	14·3%	0%	40·4%[b]

$a=\frac{50}{32}\times 22\cdot 7\%$. $b=\frac{65}{23}\times 14\cdot 3\%$.

significant difference between the survival rates within the first three to four years post enucleation and post irradiation can be due only to a difference in the selection criteria for treatment.

Char *et al.*[15] reported the results of helium ion and proton beam irradiation of choroidal melanomas. Most tumours did not show complete regression, and the mean regression in tumours two years after helium ion irradiation was no more than 31%. It seems justifiable to conclude from these findings that, after two years in the 107 patients in question, 69% of the irradiated tumour tissue had not regressed. This report indicates once more a certain insensitivity of uveal melanomas to irradiation. It must be appreciated that regression two years after irradiation of even 50% or 75% of the original volume can only delay metastatic death by one or two doubling times and cannot prevent eventual death from metastases. Only total regression can save a patient's life if metastases were absent before treatment.

The few papers which are wholly or partially based on a follow-up of more than three to four years include first those of McFaul,[22, 23] who reported a long-term clinical study on the eventual outcome of cobalt plaque therapy. The conclusion was that this therapy 'has a limited place in the treatment of choroidal melanoma, because the disease is not readily susceptible to radiation, while the incidence of major complications is high'. The second contribution is that of Lommatzsch,[21] who claimed that his results for ruthenium radiation were based on a five-year follow-up period. Analysis of this paper reveals, however, that more than 60% of the patients had actually been followed up for less than five years and in some cases for only six months. This report is therefore of doubtful relevance for the assessment of this form of radiotherapy on the survival rate. Finally, a comparison by Gass[24] of the prognosis after enucleation vs. cobalt irradiation substantiated the conclusion of McFaul. Survival figures for 27 patients treated by enucleation between June 1967 and June 1976 were compared with those of 21 patients who had been treated with cobalt-60 episcleral plaques in the same period. The combined number of large and medium sized tumours at the time of treatment was slightly higher in the enucleation group than in the cobalt-60 group. The shortest individual follow-up period was 5·5 years, the longest was 15 years, and the mean follow-up time was 10 years. After enucleation the median survival was >10 years; after irradiation it was 3·8 years. Of the enucleated patients, 22% (six out of 27) had died from metastases against 57% (12 out of 21) of the irradiated patients. Gass summarised the probability of death from metastases within five years after enucleation as 16% against 50% after cobalt irradiation.

Table 2 *Histopathology after radiotherapy*

	Number	*Tumour necrosis*	*Viable tumour*
Char *et al.*[26]*	4	2	4
von Domarus *et al.*[27]†	2	1	2
McFaul *et al.*[25]*	23	6	23
Zinn *et al.*[28]‡	1	1	1
Seddon *et al.*[29]‡	3	3	3
Char *et al.*[30]§	3	2	3
Albert[31]‡	1	1	1
Gass[24]*	5	5	4
Ferry *et al.*[32]‡	1	1	1
Total	43	22	42

*Cobalt irradiation. †Ruthenium irradiation.
‡Proton beam irradiation. §Helium ion irradiation.

The great difference in survival after enucleation and irradiation might be explained by the microscopical findings in irradiated melanomas. McFaul and Morgan[25] found absence of tumour necrosis after cobalt irradiation in 17 out of 23 eyes, while the surrounding ocular tissues showed radiation damage.

Table 2 shows that various types of radiotherapy had failed to destroy the tumour in 42 out of 43 histopathologically studied cases, which in the great majority had come to enucleation in surviving patients. These 43 cases, however, constitute a small fraction of the total number of eyes treated by irradiation and may not show that irradiation had not had a tumoricidal effect in the non-enucleated cases. The true success or failure of irradiation can be evaluated only by a long-term follow-up period. The only globe in which no viable tumour tissue is reported is included in the series published by Gass,[24] who did not provide detailed histopathological descriptions. It is noteworthy that 50% of the microscopically studied irradiated melanomas did not show any evidence of necrosis.

Two clinicopathological case reports[33, 34] claim successful treatment by irradiation. However, Grizzard *et al.*[33] describe an incomplete eye, while Cleasby and Kutzscher[34] present a one-sentence microscopic description of a choroidal mass, of which only one low-power (×25) microphotograph of an unbleached section without any cellular detail is reproduced.

It is obvious that further dissemination is excluded with certainty after enucleation. After irradiation, on the contrary, the risk of dissemination will again increase exponentially in the great majority of cases if the tumour continues to grow.

Van Peperzeel[35] has stressed that melanoma cells have a greater ability than most other tumour cells to repair the potential lethal damage induced by radiotherapy. This author also emphasised the accepted fact that poorly oxygenated tumour cells are generally less sensitive to irradiation than well oxygenated tumour cells. It is likely that a large proportion of the cells in a choroidal melanoma are poorly oxygenated. This condition thus requires high daily radiation fractions, which cause severe late damage to the normal tissue in the irradiated area.

Advocates of radiation therapy advance as their main argument the 'fight for sight' principle. The justification is that they are helping patients who can see only with the tumour containing eye. However, many patients with a healthy, functioning other eye have also been treated by irradiation. It appears that the minor visual results of this 'fight for sight', by which the patient's life is seriously endangered, do not justify the risk of unnecessary death from metastases. Lommatzsch[21] found five years after treatment a best visual acuity of ≥0·5 in 18 out of 205 irradiated eyes (8·8%). Gass[24] reported that in 15 out of 21 irradiated eyes ≥2 lines of acuity were lost and that nine of these 15 patients with ≥0·5 visual acuity at the time of treatment had ≤0·1 visual acuity at the last examination. It is necessary to reiterate that only nine out of the 21 irradiated patients in Gass's series had not died from metastases at the time the survival data were analysed.

An ideal conservative treatment should (1) eradicate the tumour, (2) retain the intact eye without prejudice to the chance of survival, and (3) preserve useful vision.[23] It is probable that none of the available radiation techniques comes up to even one of these requirements.

The present analysis indicates that patients with irradiated choroidal melanomas run the same risks that those patients with photocoagulated melanomas have incurred in the past. It has taken 20 years for Vogel[36] to be able to state that photocoagulation 'was effective only in very few specific cases'. Photocoagulation remained an experimental form of treatment for those 20 years, because no conclusive long-term results were produced. Radiotherapy has not been justified so far by any relevant long-term survival statistic. On the contrary, basic oncological knowledge, all the 10–25-year survival statistics after enucleation, and the few relevant long-term statistics after irradiation[22-24] indicate that it is medically unjustified to recommend radiotherapy to patients with a choroidal melanoma and a healthy, functioning contralateral eye. The few justifiable exceptions are elderly patients with a short life expectancy and patients who refuse enucleation. The other patients have the right to be treated by enucleation, which eliminates any further dissemination. This holds especially also for patients with small melanomas: metastatic death after enucleation of <7 mm diameter melanomas is a great rarity, but occurs in about 40% of cases within the 7–10 mm diameter size group. It is to be stressed that histopathological examination of 171 eyes, enucleated in the treatment of melanomas <10 mm diameter,[8 9 37] has confirmed the clinical diagnosis of malignant melanoma in every case. The risk of unnecessary enucleation in cases of small melanomas therefore appears to be negligible.

Seigel *et al.*[38] emphasised that, to make therapeutic progress, alternative treatments must be evaluated with well designed clinical trials or we run the risk of continuing to support inferences with inadequate studies and clinical impressions. It is justifiable to argue that it is a serious and urgent matter that those cases which have been treated by irradiation should be carefully documented and that long-term follow-up survival and functional data for irradiated uveal melanomas be published for every individual patient. Tumour related death after enucleation appeared to decrease steadily to a low percentage in the second five-year follow-up period. Our knowledge of tumour biology suggests that, after irradiation which is unsuccessful in achieving complete tumour regression, the remaining tumour tissue will continue its exponential growth. In these cases dissemination and the death rate from metastases will tend to increase exponentially in this same second five-year follow-up period. Irradiation of choroidal melanomas is still a medical experiment in which patients incur a progressive risk of death from metastases three to four years after the therapy has started.

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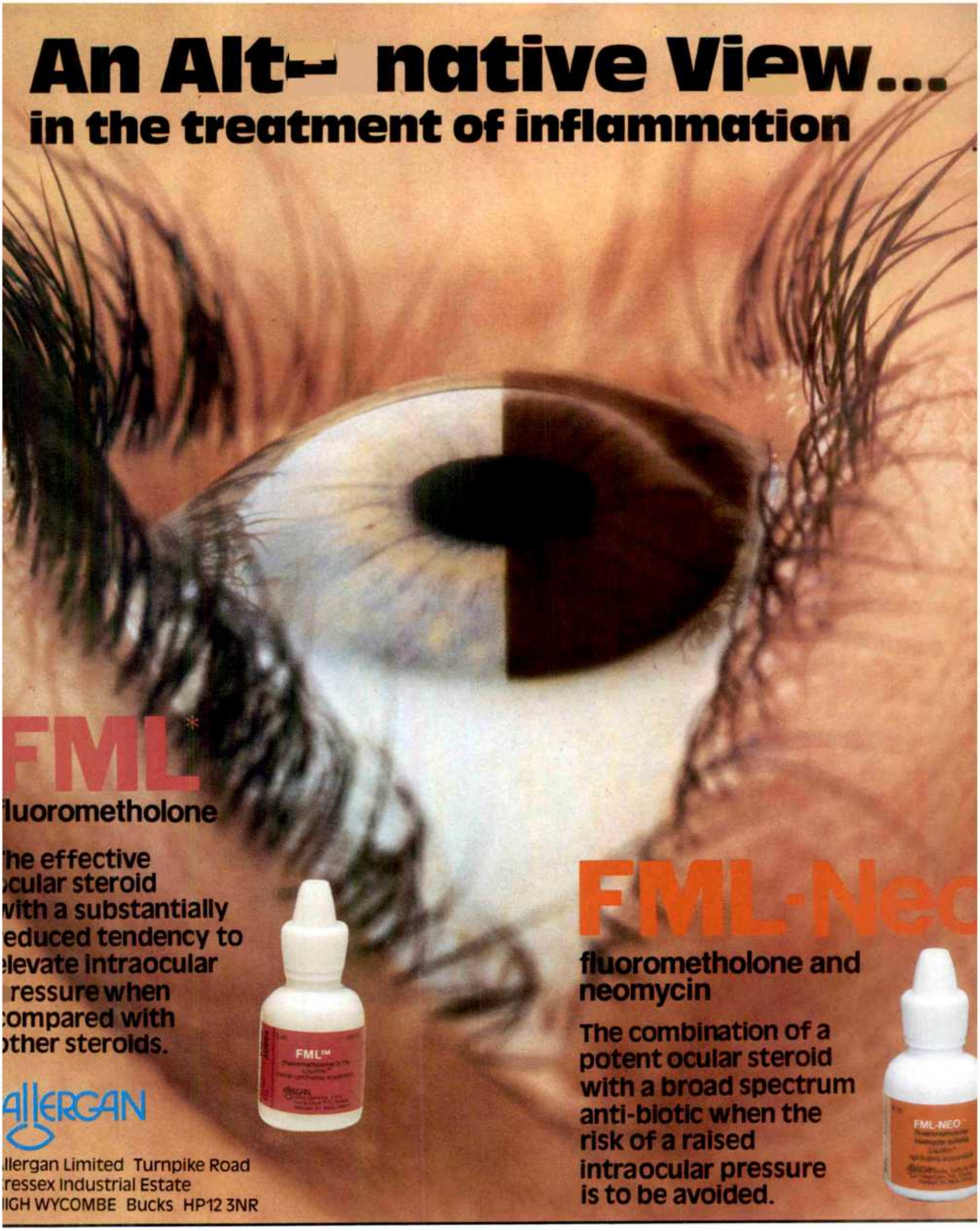

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Natural history of herpes zoster ophthalmicus: predictors of postherpetic neuralgia and ocular involvement

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SUMMARY Seventy-one patients presenting with acute herpes zoster ophthalmicus were followed up for six months for a prospective analysis of the natural history of the disease. Acute and chronic ocular complications, nasociliary nerve involvement, age, sex, rash, and pain were assessed, and the results are presented. Acute pain was measured by a visual analogue scale. Postherpetic neuralgia (PHN) was more likely in patients over 80 and in those who scored their pain highly at presentation. Duration of rash was longer in patients who developed PHN. No other associations between the parameters studied were found. Nasociliary nerve involvement was associated with subsequent ocular disease.

Ophthalmic involvement has been considered the most important and potentially serious of all sites for herpes zoster. It is reported as occuring in 33[1] to 50%[2] of cases and has the highest incidence of postherpetic neuralgia (PHN).[3] As a result it is the site that most often requires treatment, and this is usually prolonged.

A number of retrospective studies have looked at the natural history of herpes zoster. deMoragas and Kierland[3] reviewed 916 cases, of which 149 (16·3%) were trigeminal. Burgoon *et al.*[1] reviewed 206 cases, of which 36 (17·5%) were ophthalmic. Both reported a higher incidence of complications in trigeminal involvement than elsewhere. Leisegang[4] and Womack and Leisegang[5] have more recently reviewed respectively 94 and 86 patients with acute herpes zoster for ocular complications.

This study we believe for the first time prospectively analyses the natural history of acute herpes zoster ophthalmicus. In view of their high incidence and morbidity we have in addition looked for predictive indicators of ocular involvement and PHN in order to allow early identification and treatment of those patients most at risk.

Patients and methods

Between January and August 1984 53 patients presenting to the Accident and Emergency Department of St Paul's Eye Hospital, Liverpool, with acute herpes zoster ophthalmicus were examined. In addition a further 25 patients were examined at Manchester Royal Eye Hospital in the same period. Seven patients were excluded, four at Liverpool and three at Manchester: three patients could not understand standardised questions; two were taking homoeopathy at the time of presentation, rendering analysis of subsequent progression potentially unreliable; one died of an unrelated cause; one was admitted to another hospital and lost to follow-up. A total of 71 patients were studied.

Standardised assessment forms were completed at presentation and at subsequent visits. Pain was assessed by visual analogue scale (VAS). The patient was asked to look at a 100 mm horizontal line with a zero at one end and three pluses at the other, with the instruction that the latter represented the worst pain he could possibly imagine. He was then asked to indicate with a mark along the line the severity of any pain being experienced at the time of the interview, and a measurement was taken in millimeters. At subsequent interviews a fresh line was presented. Ocular involvement, nasociliary nerve (NCN) involvement at presentation, rash severity, and duration were also assessed.

Assessment of pain by a VAS has been shown to be reproducible for the same individual and a method that allows reliable statistical analysis.[6] Like all pain assessment it is subjective, and hence direct comparisons between patients cannot be made. However,

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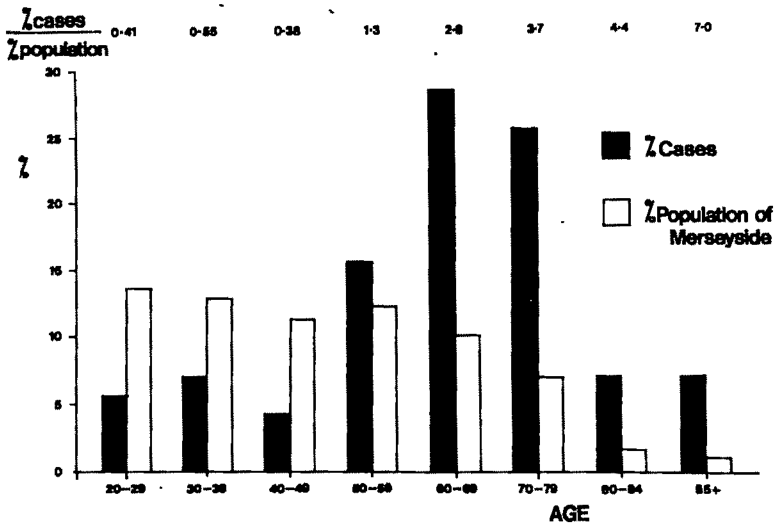

Fig. 1 *Age distribution of 71 cases of herpes zoster ophthalmicus compared with local population characteristics.*

analysis of longitudinal changes in pain for an individual are statistically valid.

After initial assessment 15 randomly allocated patients aged 60 and over were separately studied in an analysis of stellate ganglion blockade, the results of which are reported elsewhere.[7] The remaining 56 patients were followed up for six months. Ocular complications and pain were treated on their merits. PHN was defined as the presence of continuous or frequent pain at or after six months.

Results

The findings in 71 patients presenting with acute herpes zoster ophthalmicus were statistically analysed (Table 1). Mean age was 63·2 years (SD=16·64); range was 23–92.

Age distribution analysis (Fig. 1) showed a peak frequency from 60 to 69 years, but correction for local population characteristics indicated a steady rise in frequency with age. The sex distribution is also shown in Table 1. There was a highly significant predominance of male patients under 60 years old (χ^2_y=7·144; p<0·01); this was more pronounced under 40 years (χ^2_y=9·690; p<0·01) (the y denotes that Yates's correction was applied).

Thirteen patients were pain free at presentation (18·3%). No patients had malignant disease at presentation or during subsequent follow-up. The ocular complications noted in 71 patients excluding conjunctivitis are listed in Table 2. One patient developed contralateral disease with rash three months after initial presentation; at that time there was active keratouveitis on the initially affected side but no subsequent involvement of the fellow eye occurred.

Fifteen patients aged 60 and over, randomly allocated at presentation to treatment with stellate ganglion block were then excluded, and analysis of the remaining 56 is presented below.

OCULAR INVOLVEMENT

Twenty-eight of 56 patients developed ocular complications (50%). The mean time of onset was 1·82 weeks after the onset of the rash, with a range of one to four weeks. When related to age (Table 1) there

Table 1 *Factors associated with herpes zoster ophthalmicus compared with age*

Age	*Overall group*	*Sex*		*Untreated group*	*Ocular involvement*				*Rash*		*Acute pain (mean VAS)*			*PHN*	
		M	*F*		+	–	*Mean onset (weeks)*	*Chronic*	*Mean severity*	*Mean duration (days)*	*Presentation*	3/52–1/12	9/52–3/12	+	–
20–39	9	8	1	9	6	3	1·00	0	2·22	17·56	38·89	8·72	4·33	1	8
40–59	14	6	8	14	4	10	1·25	1	1·71	20·78	36·50	20·08	5·62	1	13
60–79	38	10	28	26	12	14	2·25	6	1·89	23·62	37·69	31·67	20·83	5	21
80+	10	2	8	7	6	1	2·17	1	2·29	24·71	37·00	31·58	34·75	5	2
Total	71	26	45	56	28	28		8						12	44

Table 2 *Nature of ocular complications in 71 patients*

Anterior uveitis	33
Keratitis	16
Disciform keratitis	9
Neuropathic corneal ulcer	3
Secondary glaucoma	2
Cranial nerve palsy	2
IVth nerve	1
VIth nerve	1
Contralateral herpes zoster ophthalmicus	1
Orbital apex syndrome	1
Total involved	36

was a difference in mean time of onset of involvement between those under 60 (1·10 weeks) and those aged 60 and over (2·23 weeks), and this achieved a high level of significance (t=9·379; p≪0·001). There was no significant difference in incidence of ocular involvement in relation to age: under 40 compared with over 40 (χ_y^2=0·530; p>0·1); under 60 with over 60 (χ_y^2=0·295; p>0·5); under 80 with over 80 (χ_y^2= 2·613; p>0·1). There was no significant difference in incidence of ocular involvement between the sexes (χ_y^2=0) (Table 3).

Treatment of keratitis and uveitis was initially with acyclovir ointment, and topical steroids were introduced only later in severe unresponsive cases and in several of those which went on to chronicity.

Ocular involvement when still active at six months was defined as chronic and occurred in eight of 28 initially involved patients (28·6%). Chronic eye disease occurred in 14·3% of the 56 patients studied, with an age range of 54–91. However, the difference in incidence between those under 54 and those aged 54 and over did not achieve significance (χ_y^2=2·734; p>0·05). Seven patients had keratouveitis still active at six months, two of these with an associated secondary glaucoma; a further three had neuropathic corneal ulcers. All had chronic anterior uveitis.

NASOCILIARY NERVE

NCN involvement was assessed at presentation and was defined as involvement by rash of the external nasal nerve. It occurred in 21 of 56 patients (37·5%). There was a highly significant association between presence of NCN involvement at presentation and the subsequent development of ocular complications (χ_y^2=7·619; p<0·01) (Table 3). If NCN involvement existed at presentation, there was a 76·2% chance of subsequent ocular involvement. If there was no NCN involvement at presentation, there was only a 34·3% chance of the eye developing complications.

Table 3 *Factors related to ocular involvement*

Ocular involvement	*Sex*		*NCN*		*Mean rash severity*	*PHN*	
	M	*F*	+	−		+	−
+	13	15	16	12	2·04	7	21
−	12	16	5	23	1·86	5	23

There was no significant association between NCN involvement and chronicity of ocular complications in already involved eyes (χ_y^2=0·616; p>0·1).

RASH

Severity of rash was estimated on a 1–3 scale, 1 representing mild, 2 moderate, and 3 severe. There was no significant difference between severity of rash and age: under 40 compared with 40 and over (t=1·365; p>0·1) (Table 1). There was no significant difference between rash severity in patients who went on to develop ocular involvement compared with those who did not (t=0·924; p>0·1). (Table 3).

Duration of rash was measured by duration of crusts in days, with a mean of 22·0 days and a range of 6–35 days. The mean duration of rash in each age group (Table 1) increased with age. Patients under 40 had a significantly shorter duration of rash than those aged 40 and over (t=2·292; p<0·05), and this held for those aged under 60 and 60 and over (t=2·489; p<0·02).

PAIN

Ten patients out of 56 were pain free at presentation (18%). Six of these developed pain at some time later (60%) and two of these went on to develop PHN. Four of the 56 patients (7%) were pain free throughout the course of the disease.

Table 1 shows the mean VAS scores at presentation and during subsequent time bands for each of four age groups. For the 20–39 age group the mean VAS scores fell dramatically by two weeks' to one month (p<0·01), while this fall had occurred only by six weeks to three months for the 40–59 age group (p<0·01). For the 60–79 age group there was a fall in mean VAS by six weeks to three months, but this was of lesser significance (p<0·05). For the patients aged 80 and over there was no significant fall at any time during the acute phase (p>0·05).

An analysis was performed by comparing pain scores at presentation with those in subsequent time bands within each group by paired t tests.

Table 4 shows that compared with presentation there was a fall in incidence of pain at each subsequent time band. This achieves significance by six weeks to three months (χ_y^2=12·72; p<0·001) and is very highly significant by six months (χ_y^2=41·34; p≪0·001).

POSTHERPETIC NEURALGIA

Twelve of the 56 patients developed PHN (21%).

Table 4 *Factors related to the development of postherpetic neuralgia*

PHN	*Sex*		*Chronic eye disease*		*NCN*		*Rash*		*Mean onset ocular involvement (weeks)*	*Mean VAS at presentation*	
	M	*F*	*+*	*−*	*+*	*−*	*Mean severity*	*Mean duration (days)*		*All ages*	*Over 60*
+	5	7	2	5	2	10	2·17	25·08	2·20	47·42	53·10
−	20	24	6	15	19	25	1·88	21·25	1·71	34·80	30·78

Factors that might influence or be associated with this development were sought.

Age. The mean age for those patients who developed PHN was 70·75 years (range 25–92). This was significantly higher than those who did not—58·34 years (t=2·242; p<0·05). Table 1 shows the incidence of PHN related to age. 30% of patients aged 60 and over were afflicted, while the incidence rose to 71% at 80 and over. There was a highly significant difference in incidence of PHN between patients under 80 and those 80 and over (χ_y^2=8·727; p<0·01), but a significant difference did not occur at lower ages.

Sex. There was no significant difference in incidence of PHN between the sexes (χ_y^2=0·0088 p>0·05). This non-significance did not change when only patients over 60 were analysed (χ_y^2=0·01; p>0·5) (Table 4).

Ocular involvement. This was not significantly associated with PHN (χ_y^2=0·002; p>0·5) (Table 3). PHN was not associated with chronic eye disease (χ_y^2=0·001; p>0·5) (Table 4). Mean time of onset of ocular involvement after onset of rash was greater in those who developed PHN, but this did not achieve significance (t=0·962; p>0·1).

Nasociliary nerve involvement. This was not associated with subsequent development of PHN (χ_y^2=1·576; p>0·1) (Table 4).

Rash. Duration of rash was longer in those patients who developed PHN but this was not significant (t=1·793; p>0·05) (Table 4). Severity of rash was greater in those who developed PHN but was also not significant (t=1·195; p>0·1).

Acute pain. Mean VAS scores at presentation were higher in those patients who subsequently developed PHN (Table 4). This was significant for patients aged 60 and over (t=2·204; p<0·05) but not for the whole group (t=1·402; p>0·1). However, VAS scores of 35 mm and over at presentation were significantly associated with PHN when compared with scores below 35 mm (χ_y^2=5·197; p<0·05). This was also true of comparisons between scores of under 30 mm and those of 30 mm and over (χ_y^2=4·023; p<0·05), under 40 mm with 40 mm and over (χ_y^2=4·773; p<0·05), and under 50 mm with 50 mm and over (χ_y^2=4·095; p<0·05).

Table 5 shows that the mean pain score falls highly significantly by six weeks to three months in those patients who did not develop PHN but stayed high in those who did (paired t tests). The presence of pain at two weeks to one month was not associated with the development of PHN (χ_y^2=0·148; p>0·5) but the presence of pain at six weeks to three months was, and this highly significantly (χ_y^2=8·680; p<0·01).

Discussion

Frequency of infection increased with age until 70 and decreased thereafter, but with population correction there was a steady rise in incidence (Fig. 1), conforming with previous work.[1,3,8,9] No cases were seen below age 20, supporting the similar findings of Burgoon *et al.*[1] and deMoragas and Kierland.[3] However, Edgerton[2] found several reports of ophthalmic zoster in infancy and concluded that there are two periods in life in which infection is most likely—under 14 and over 40. It is possible that some affected infants may have been referred elsewhere during our study, explaining the lack of young cases. However, it is certain that infantile ophthalmic zoster is uncommon in the healthy population. The mechanism of infection in this age group is usually exposure to varicella zoster virus in utero at the time of maternal chickenpox.[10]

Of the 71 patients 63·4% were female, and this is consistent with previous reports.[1,5] However, our age distribution analysis shows that under age 60 there is a highly significant increase in the number of males involved, while female cases were more likely among patients aged 60 and over.

Ocular complications seen in herpes zoster ophthalmicus have been well documented[4,5,8,11–18] and occurred in 50% of our patients. Anterior uveitis was

Table 5 *Mean VAS scores at presentation and subsequent time bands compared with subsequent onset of PHN*

PHN	*Presentation*	*2/52–1/12*	*6/52–3/12*
+	47·42	38·75 p>0·10	34·50 p>0·10
−	34·80	23·14 p>0·05	10·67 p<0·001

commonest, occurring in 92% of patients with ocular involvement, followed by corneal complications in 52%. These two accounted for the great majority, and all but two cases of corneal disease were associated with an underlying uveitis. Disciform keratitis occurred in 25% of involved eyes and is approximately twice the incidence reported by Leisegang[4] and Marsh.[11,12]

Ocular motor palsies occurred in two patients and have been reported previously.[8,16,17] Most series report a lower incidence, but Marsh *et al.*[17] found a much higher 31% of new cases after careful examination, with several being contralateral or bilateral and third nerve involvement the commonest. As is typical, both our cases resolved spontaneously and completely.

One patient developed orbital apex syndrome seven weeks after the onset of the rash, with combined external ophthalmoplegia, proptosis, and ptosis. Treatment with indomethacin was begun, with a rapid improvement in orbital signs, but three months later the disc was atrophic and the best vision was 6/36. Marsh[11,17,19] suggested the use of systemic steroids in these cases in order to reduce the occlusive vasculitis which is the probable underlying mechanism.

Ocular complications not seen in our series but reported elsewhere include nodular episcleritis and scleritis, third nerve palsies, and several corneal manifestations including mucous plaque keratitis, nummular keratitis, perforation, and interstitial keratitis.[4,5,10–18,20]

The development of ocular complications was not related to age, sex, or severity of rash but did occur about one week later in the patients aged 60 and over. Nasociliary nerve involvement at presentation was strongly associated with subsequent development of ocular complications (76·2%), as was the converse. This has been suggested previously[11] but never subjected to statistical analysis.

Rash severity was not related to age, but duration of rash was significantly shorter in younger patients, especially under 40.

Much emphasis has been placed in the past on detailed and thorough investigation of all new cases for underlying malignant disease, especially lymphomas.[3] Recent work has indicated the futility of this by showing that no previously undiagnosed malignancy is likely to be found at onset[21] and that on long term follow-up the annual incidence of new malignant lesions is similar to that in the normal population.[22] Our series lends support to this, as no cases of malignant disease were noted at any stage.

Acute pain associated with herpes zoster ophthalmicus is distinct from the later development of postherpetic neuralgia. This study shows that acute pain as measured by VAS decreases with time, and this more rapidly in younger age groups. It is common at presentation, occurring in 82·1% of patients. Of those who were pain free at presentation 60% subsequently developed pain. It is therefore apparent that the great majority experience pain at some time.

The incidence of PHN in this study was 21·4%. This is much higher than the 7% reported by Marsh[11,19] and the 9·7% reported by Burgoon *et al.*[1] It is more in keeping with the higher incidence reported by deMoragas and Kierland.[3] The development of PHN in one patient aged 25 indicates that, though less common, this is an important complication in younger patients. One patient had no pain until the onset of PHN at six months; one should not assume that the absence of acute pain implies the eventual freedom from PHN.

This study shows that patients aged 80 and over have a significantly higher chance of developing PHN than younger patients. A high VAS pain score at presentation in patients aged 60 and over was significantly associated with PHN. Analysis suggests that a high index of suspicion should be given to presentation scores in excess of 35 mm. There was a very highly significant fall in VAS scores by six weeks to three months in those who did not develop PHN, while for those who did the scores stayed high. Furthermore the presence of pain in this time band was highly significantly associated with PHN.

No association was found between PHN and ocular involvement, chronic eye disease, duration or severity of rash, sex, or nasociliary nerve involvement at presentation.

This study shows that PHN is more likely in older patients and in those who score their pain highly on VAS at presentation. These two factors therefore allow some measure of prediction of which patients should be treated. As our and other work has shown this should be early, preferably before 14 days. Furthermore the failure of VAS scores to fall as the condition progresses should alert the clinician to the impending development of PHN, one of the most severe complications of this disease.

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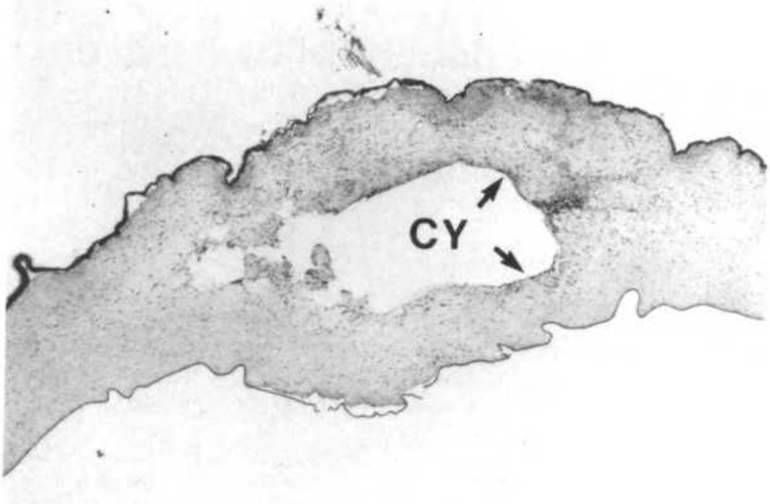

Fig. 1 *A large cystic space* (CY) *is present in the central cornea. Several layers of keratocytes (arrows) line a portion of the cavity. Small interruptions in Descemet's membrane posterior to the cyst are artefact. Haematoxylin-eosin.*

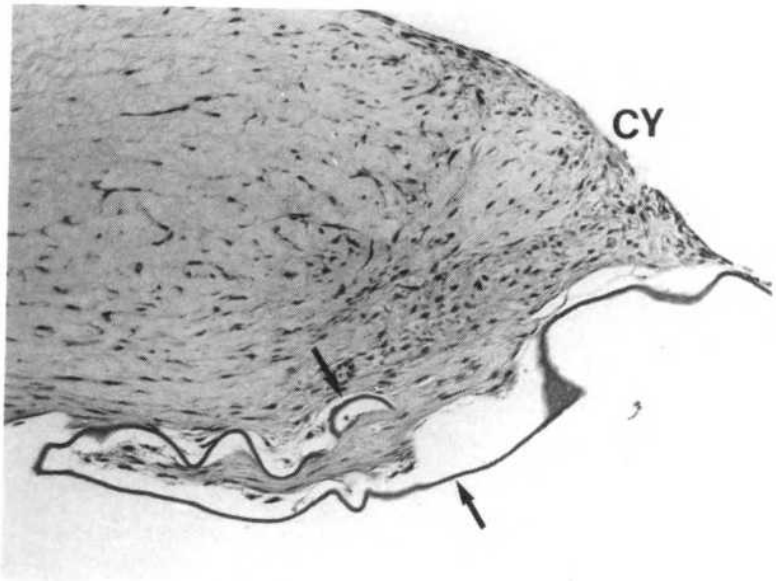

Fig. 2 *An extension of the stromal cyst* (CY) *could be traced posteriorly to a break in Descemet's membrane (arrows). No endothelial cells are present in this section. Haematoxylin-eosin.*

tion was the result of uncontrolled influx of aqueous into the corneal stroma through rents in Descemet's membrane. Since the pseudocyst in our patient could not be delineated through the opacified stroma, the stroma anterior to the cyst was mistakenly interpreted as being the total thickness of a severely ectatic cornea. A review of keratoconus and of related non-inflammatory corneal thinning disorders did not describe pseudocyst formation as a complication of hydrops.[4] We are unaware of any previous reports describing the occurrence of pseudocyst formation in this clinical setting.

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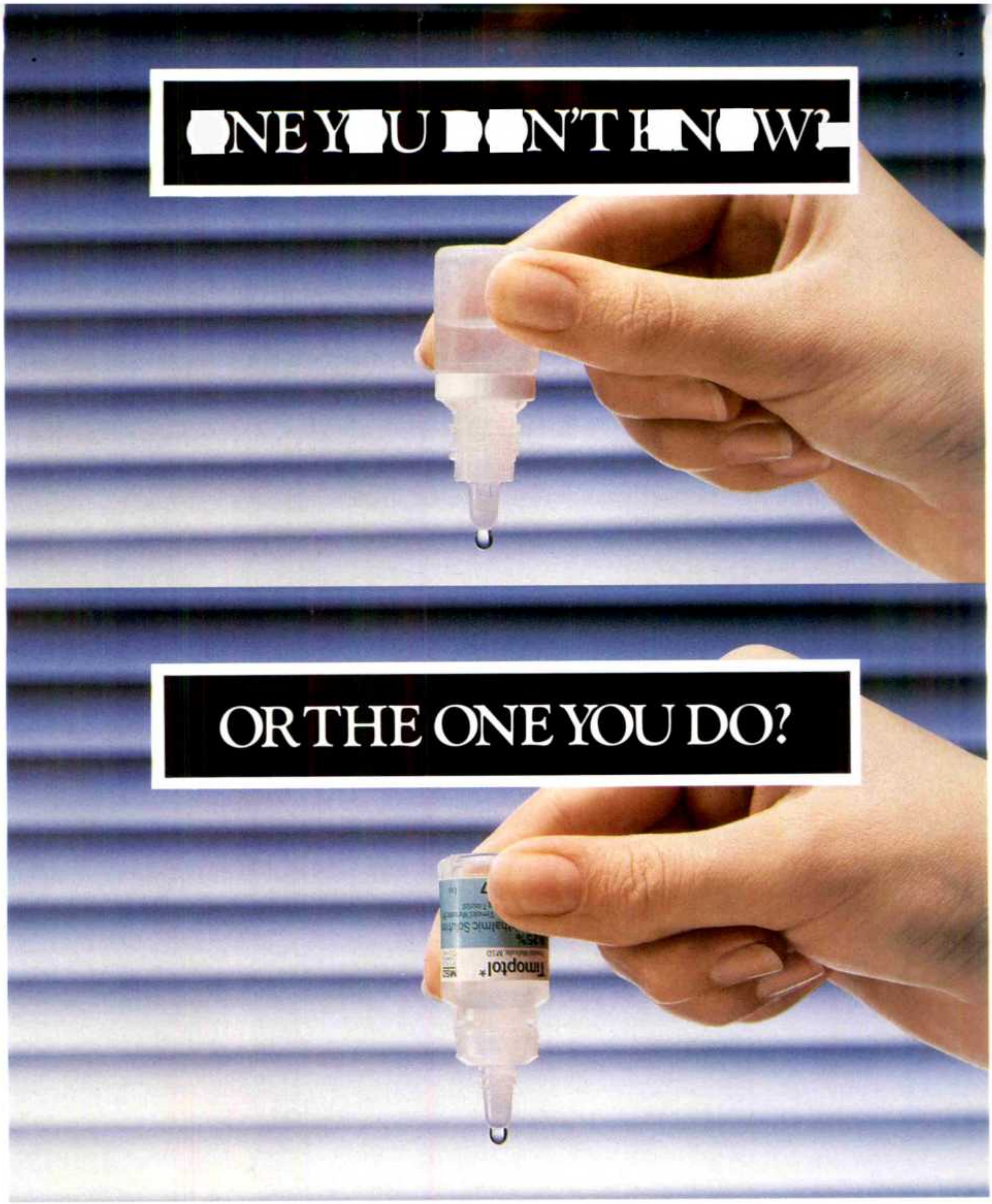

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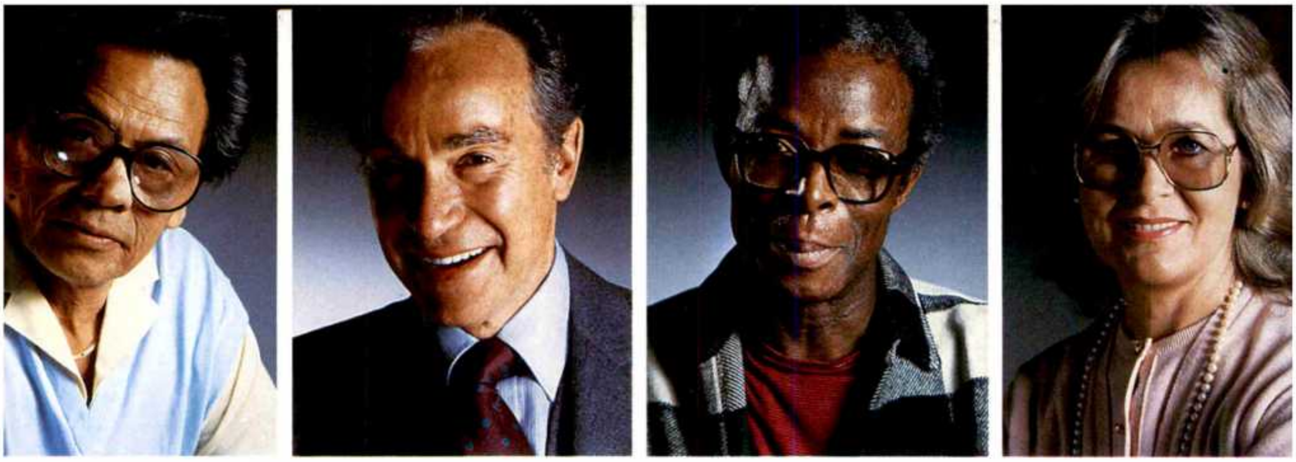

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Assessment of activity of ocular sarcoidosis by gallium scanning

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SUMMARY Gallium (^{67}Ga) citrate uptake over the orbits, parotid glands, and lungs was examined in six newly detected patients with sarcoidosis and 17 with chronic sarcoidosis. Six of 23 (26%) had uveitis, 18/23 (78%) decreased lacrimal secretion, and 13/16 (81%) epithelioid cell granulomas in conjunctival biopsies. Ten patients with other diseases served as controls. Only five patients had ocular complaints and two had enlarged parotid glands. ^{67}Ga uptake over the orbits and parotids was measured by a quantitative computer based method. Gallium uptake was significantly higher over the orbits ($p<0{\cdot}001$) and parotids ($p<0{\cdot}01$) in the newly detected patients and in the parotids ($p<0{\cdot}01$) in the chronic group than the corresponding uptake in the controls. We suggest that in sarcoidosis an increased ^{67}Ga uptake in the orbital and parotid areas may be a phenomenon comparable to an increased ^{67}Ga uptake in the lungs in active alveolitis. Gallium scan is a good method for revealing even symptomless ophthalmic sarcoid changes. However, in chronic sarcoidosis an equal or only slightly increased gallium uptake over the orbits compared with background activity does not exclude ocular sarcoid disease.

Epithelioid cell granulomas are the histological hallmark of sarcoidosis. However, recent studies[1 2] have shown that activation of immune cells precedes and modulates the formation of the granulomas. Studies with radioactive gallium (^{67}Ga) have added to the knowledge of the pregranulomatous cell mechanisms. In sarcoidosis ^{67}Ga has been shown to be taken up by 'activated' macrophages of pulmonary alveoli.[2] The studies concerning mainly pulmonary changes have also revealed that besides lung areas gallium accumulates often in localised extrathoracic sites, for example, in lacrimal and parotid glands.[3-5]

Only a few ophthalmological studies have attempted to clarify the phenomenon of gallium uptake over the orbito-parotid areas in sarcoidosis. Weinreb *et al.*[6 7] showed that, irrespective of an ocular sarcoid disease, ^{67}Ga accumulated in the lacrimal glands in sarcoidosis. Karma *et al.*[8 9] suggested that in ocular sarcoidosis confirmed by conjunctival biopsies both ocular and parotid areas accumulate radiogallium.

We examined gallium ^{67}Ga citrate uptake over the orbits, parotids, and lungs in patients with newly detected untreated sarcoidosis and patients with chronic sarcoidosis with concurrent ophthalmic sarcoid changes. The intensity of the gallium activity was calculated by a semiquantitative computer based method.

Materials and methods

Twenty-three patients with generalised active sarcoidosis, six of recent onset and 17 chronic cases, and 10 controls were selected for the study. The diagnosis of sarcoidosis was based on a typical clinicoradiological picture and was confirmed histologically in every patient (by mediastinoscopy, biopsy of bronchial mucosa or skin, or by the Kveim test).

Group 1: Newly detected sarcoidosis. This group consisted of six patients whose sarcoidosis at the time of gallium scanning had been diagnosed less than 12 months previously. Five patients were referred by a chest physician for an ophthalmic examination because of marked gallium accumulation seen over the orbits and parotid areas. They had no ocular complaints, but two had enlarged parotid glands bilaterally. One patient (case 1) had a history of

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Table 1 *Ophthalmic findings in sarcoidosis patients*

Type of sarcoidosis	*Positive conjunctival biopsy*		*Lacrimal gland disease**		*Active uveitis*		*Total no. of patients*
	%	*No.*	%	*No.*	%	*No.*	*No.*
Newly detected cases	75	(3/4)	67	(4/6)	33	(2/6)	6
Chronic cases	83	(10/12)	82	(14/17)	23	(4/17)	17
Total	81	(13/16)	78	(18/23)	26	(6/23)	23

*Assessed by Schirmer's I test.

neurological symptoms, weight loss, and malaise for three years. Her sarcoidosis, Heerfordt's syndrome, was of chronic type, though the diagnosis was delayed. All the patients had pulmonary sarcoid x-ray changes. Angiotensin converting enzyme (ACE) was increased in four patients. The mean ACE was 96·5 U/l (range 40–155 U/l, normal range 25–80 U/l). None had received oral or topical steroids (eye drops) by the time of the gallium scan.

A detailed ophthalmological examination included measurement of visual acuity, eye movements, biomicroscopy of the anterior segment of the eyes, measurement of ocular pressure, ophthalmoscopy, and three-mirror-glass examination of the peripheral fundus. Lacrimal secretion was examined by Schirmer I testing after preliminary biomicroscopy of the eyes. Lacrimal secretion was assessed as decreased when the length of the moistened test strip was <7 mm. A conjunctival biopsy specimen was taken from a suspicious nodule, if seen, otherwise from the normal looking conjunctiva of the lower fornix by the method described previously.[10] The sections were stained with haematoxylin-eosin. Epithelioid cell granulomas under an intact epithelium were interpreted as having been produced by sarcoidosis.

The ophthalmological examination of the newly detected patients revealed conjunctival granulomas in three out of four biopsied cases, decreased lacrimal secretion in four, and uveitis in two patients (cases 1 and 2) (Table 1).

Group 2: Chronic ocular sarcoidosis. This group consisted of 17 patients who, after a personal follow-up (by AK) of 10 years on the average, still had one or more of the following ocular sarcoid findings: conjunctival granulomas in 10 of the 12 biopsied cases, decreased lacrimal secretion in 14, and active uveitis in four (Table 1). Only five patients had symptoms of their ocular sarcoid change: three of uveitis and two of decreased lacrimal secretion. Two patients with a negative conjunctival biopsy during the first years of the disease had developed conjunctival granulomatosis by the time of the present study. One patient with a positive conjunctival biopsy initially had no suspicious lesions in the conjunctivae at the present follow-up examination and the biopsy was negative. Four positive conjunctival biopsies disclosed fibrous tissue round the epithelioid cell aggregates (Fig. 1).

All the patients with a decreased lacrimal secretion considered to be of sarcoid origin during the time of the diagnosis of the disease still had it at the time of this study. Seven patients had initially had uveitis. In three of them uveitis had become inactivated by the time of this study. At the onset of the disease one

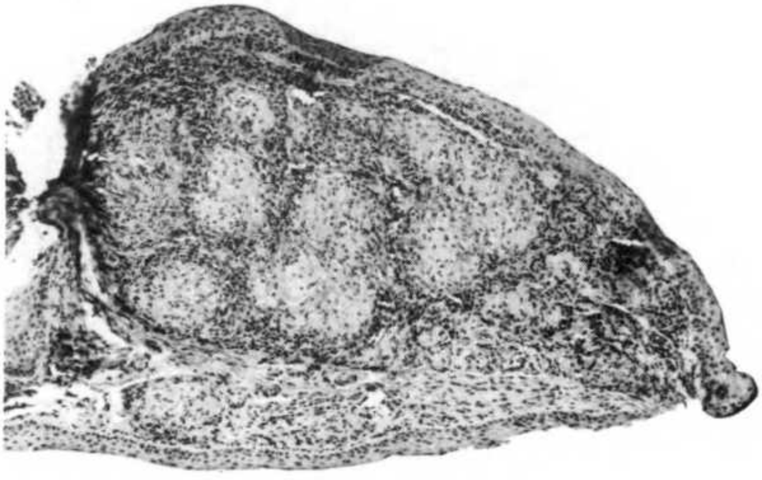

Fig. 1 *Conjunctival sarcoidosis. Epithelioid cell granulomas surrounded by fibrous tissue in a patient with chronic sarcoidosis. Haematoxylin and eosin.*

patient had had uveoparotid fever. The parotids had become normal in size within a year, but nine years later uveitis was still running a very active course. In addition two patients without uveitis but with conjunctival granulomatosis and lacrimal gland disease had had a transient enlargement of the parotid glands during the first months of the disease.

Either initially or some years after the onset of the disease all the patients had had pulmonary *x*-ray changes. In seven patients the *x*-ray changes had resolved by the time of the gallium scanning.

Twelve of the 17 patients in this group had increased or borderline ACE. The mean ACE was 83·5 U/l (range 16–184 U/l). In five patients with normal ACE the disease showed clinical activity: uveitis, enlarging skin lesions, or deterioration of the pulmonary function tests.

Ten patients had received oral prednisolone for two to 92 months, and seven patients had received topical steroids during the years of the follow-up. Three patients received dexamethasone eye drops at the time of the scanning, but none were on oral steroids.

Group 3: Controls. Gallium scan was also performed on 10 control patients, seven with chronic bronchitis, asthma, or allergic alveolitis and three with ocular complaints (one with uveitis and two with suspicion of sicca syndrome). Sarcoidosis was excluded in all of them.

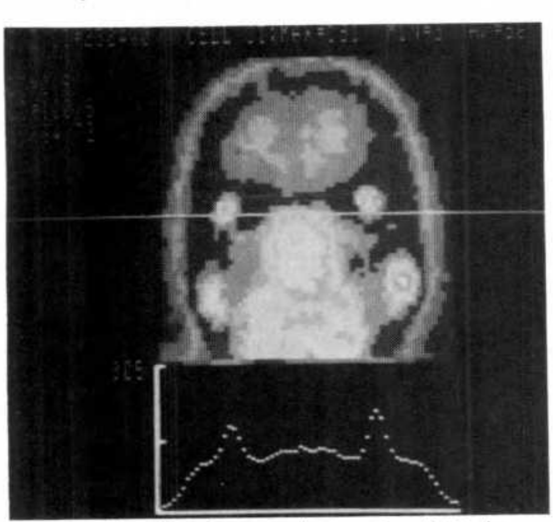

Fig. 2 *Gallium ^{67}Ga citrate uptake over the orbits in the anterior view of the head as seen in the gamma camera computer screen. The area round the horizontal line crossing the orbits was used for the construction of the activity profile by the computer. Height of the area was 2 or 3 pixel lines having the maximum activities (maximum number of counts per pixel) of the orbits. The activity profile (amount of activity in the vertical scale and location of the activity in the horizontal scale) is shown in the lower part of the figure. Gallium uptake over the orbits (the two peak activities of the profile) were expressed in percentages of the minimum background activity (100%) of the profile between the orbits. Relative uptake of the parotid glands was calculated similarly from a horizontal activity profile crossing the parotid glands.*

SCANNING TECHNIQUE

Each patient received 1·5 MBq/kg ^{67}Ga citrate intravenously 48 h prior to scanning. Anterior views were obtained of the head, chest, and upper abdominal regions with a wide scanner (Siemens, Rota-Camera ZLC-75) and analysed by the Gamma-11 computer system. Using anterior views of the head the computer constructed two horizontal activity profiles of gallium uptake, one crossing the orbits (Fig. 2) and the other the parotid glands. The activity profiles comprised two or three vertical pixel lines having the maximum activity (maximum number of counts per pixel) of the orbits and the parotid glands respectively. Gallium uptake of the orbits and the parotid glands was expressed in percentages of the minimum background activities (100%) of the profiles between the orbits and parotid glands respectively (Table 2).

Uptake in the lung hila and parenchyma was graded from 0 to 3 relative to liver activity (classification proposed by several investigators[1 3 11]). Grade 0 signified uptake comparable to background activity; grade 1 uptake greater than background but less than liver activity; grade 2 uptake equal to, and grade 3 uptake greater than, liver activity.

Table 2 *^{67}Ga uptake over the orbits, parotid glands and lungs in sarcoidosis patients and controls**

Classification of the groups	*Gallium uptake**				
	Orbits (%)		*Parotids (%)*		*Lungs*
	Mean†±sd	*Range*	*Mean†±sd*	*Range*	*0 1 2 3*
Newly detected sarcoidosis (n=6)	252±69§	164–355	191±93‡	100–418	1 2 3
Chronic sarcoidosis (n=17)	146±27	100–206	145±38‡	100–221	10 3 4
Controls (n=10)	142±27	112–177	104±10	100–128	10

*Uptake of the orbits and the parotid glands was expressed in percentages of maximum activity (number of counts per pixel) out of the minimum background activity (100%) in the horizontal activity profile between the orbits and parotid glands, respectively. Uptake by the lungs was graded 0–3 relative to liver activity. Grade 0 signified uptake comparable to background activity; grade 1 uptake higher than background but less than liver activity; grade 2 uptake equal to, and grade 3 uptake higher than, liver activity.

†The average activity of the two orbits and two parotids, respectively.

‡Significantly ($p<0·01$), §highly significantly ($p<0·001$) different from the control value by Student's *t* test.

Results

The relative intensity of the gallium uptake over the orbits, parotids, and lungs in the three groups are shown in Table 2. The ^{67}Ga uptake over the orbits in the newly detected patients with sarcoidosis significantly exceeded the corresponding ^{67}Ga uptake in the chronic patients and controls ($p<0\cdot001$ by Student's *t* test). The ^{67}Ga uptake of the parotid areas in both the newly detected ($p<0\cdot001$) and the chronic ($p<0\cdot01$) sarcoidosis patients significantly exceeded the corresponding activities in the controls. The difference in the values of the parotid uptake between the newly detected patients and the chronic ones was not significant ($p<0\cdot5$). All the newly detected sarcoidosis patients showed an increased lung uptake (grade 1 to 3). In 10 patients of the chronic group and in all the controls the lung uptake was not increased. One patient in the newly detected group with an orbital uptake of 170% showed an uptake of 100% by the parotids. She had a bilateral hilar adenopathy on *x*-ray, erythema nodosum, and no sarcoid changes were found in the ophthalmological examination. The heaviest ^{67}Ga uptake by the parotids among the newly detected patients was seen in the patient with Heerfordt's disease (case 1). She had the lowest lung uptake in this group.

None of the chronic patients had a mean uptake over the orbits greater than the corresponding mean uptake in the new cases (252%), but in four chronic patients the parotid uptake exceeded the corresponding mean uptake in the new cases (191%).

In three patients gallium scanning was done twice. In one patient with a chronic sarcoidosis the scanning had been performed eight months before the present study, and in two new patients the scanning was repeated six months and eight months after the first procedure. These cases are briefly reported.

CASE 1

A 56-year-old woman had for three years experienced weight loss, malaise, increasing tremor and rigidity, and transient facial palsies. She was referred for an ophthalmological examination because of complaints of decreasing vision and constriction of the visual fields. The left facial nerve was weak and the submandibular and parotid glands were enlarged and warm on palpation. Her visual acuity was 20/100 in the right and 20/40 in the left eye. Lacrimal secretion was decreased to 1 mm in both eyes. Granulomatous bilateral uveitis was seen. Intraocular pressure was 30 mmHg in both eyes, and the optic discs showed glaucomatous cuppings. Visual field examination disclosed marked defects compatible with glaucomatous changes. ACE was 124 U/l. Lysozyme was 21 mg/l (normal range 3–9 mg/l). A tuberculin skin test to 100 tuberculin units was nonreactive. Chest *x*-rays showed parenchymal infiltrations. Conjunctival biopsy was negative. Biopsy of the skin lesion of the forehead showed noncaseating granulomatous inflammation. Sarcoidosis with a classical Heerfordt's syndrome was diagnosed. Gallium scan (Fig. 3) showed ^{67}Ga uptake to 223% over the orbits and 418% in the parotid areas respectively, but only slightly increased lung uptake (grade 1). With topical corticosteroids the uveitis became quiescent and the pressure became normal. Systemic corticosteroids had to be restricted because of their psychogenic side effects. Six months later the gallium images of the head and chest were unchanged.

CASE 2

A 37-year-old man with pulmonary sarcoidosis was referred to an ophthalmological examination because, in addition to an increased lung uptake (grade 3), an increased ^{67}Ga uptake of the orbital and parotid areas was seen (Figs. 4A, B). Mean gallium uptake over the orbits was 250% and that of the parotids 175%, respectively. He had no ocular complaints. Visual acuity was 20/20 in both eyes. Lacrimal secretion was decreased to 1 mm in the right and 5 mm in the left eye, and a peripheral uveitis was seen. Examination of the conjunctivae showed isolated yellowish nodules typical of sarcoidosis. On biopsy they were found to contain epithelioid cell granulomas. The patient received oral and topical

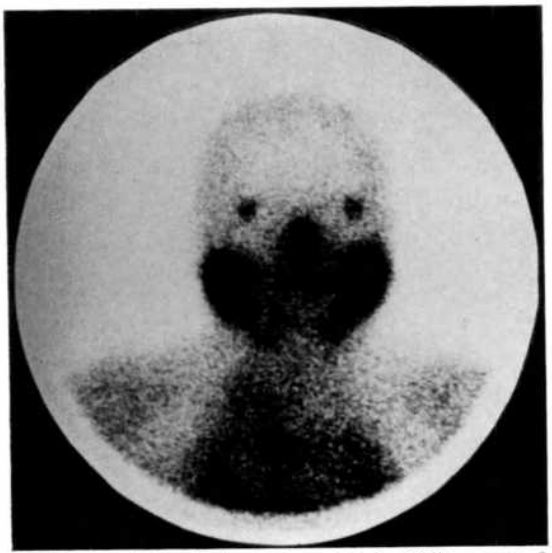

Fig. 3 *Case 1. Newly detected sarcoidosis. Gallium scan of the head showing a highly increased ^{67}Ga uptake over the orbits (223%) and parotid glands (418%) in a 52-year-old woman with a classical uveoparotid fever.*

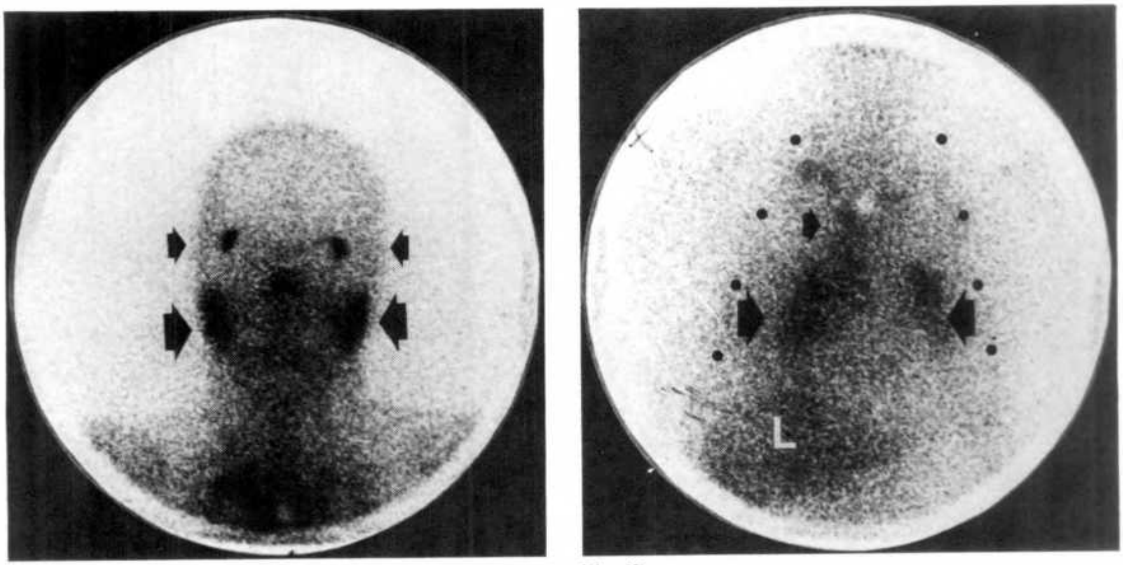

Fig. 4A

Fig. 4B

Fig. 4 *Case 2. Newly detected sarcoidosis. Gallium scan showing an increased* ^{67}*Ga uptake* (A) *over the orbits (250%), parotids (175%) (arrows), and* (B) *lungs (grade 3) (arrows) in a 30-year-old man with subclinical uveal, conjunctival, and lacrimal gland sarcoidosis. Thoracic contours are marked with dots. L=liver.*

corticosteroids for one month. In a follow-up examination six months later the lacrimal secretion became normal. There was no uveitis, but sarcoid nodules were still seen in the conjunctivae. The gallium images showed much decreased activity over the orbits (187%) and parotids (114%) and no activity in the lung areas (grade 0).

CASE 3

A 52-year-old woman had had in the 1950s a right parotidectomy because of malignant disease. Pulmonary sarcoidosis was diagnosed in July 1980. Since then she had been receiving oral prednisolone beginning with a dose of 20 mg/day. ACE was initially 170 U/l but decreased to a normal range in three months. *X*-ray changes and pulmonary symptoms deteriorated in October 1982. Visual acuity was 20/40 in the right eye and 20/25 in the left eye, and a symptomless uveitis was seen in both eyes. Gallium scan showed an increased uptake over the orbits (157%) and left parotid (208%), but the lung uptake was not increased (grade 0) (Figs. 5A, B). ACE rose to 106 U/l after the prednisolone was discontinued in February 1983. Ophthalmic examination showed reactivation of uveitis bilaterally and nodes in the left iris (Fig. 6A). Lacrimal secretion had ceased (1 mm in both eyes). Conjunctival biopsy gave negative results. This time gallium images showed increased activity in lung areas (grade 3) (Fig. 6B), but the uptake over the orbits and the left parotid was of the same magnitude as eight months previously.

Discussion

Gallium scanning is a sensitive method for revealing active pulmonary sarcoidosis.[1-5] But it is an unspecific method, for ^{67}Ga citrate has been shown to accumulate also in a wide variety of inflammatory and neoplastic thoracic and extrathoracic sites.[12 13] Gallium uptake over the orbits or parotids is not specific for sarcoidosis either. An increased uptake in these areas can be seen, for example, in Sjögren's syndrome, lymphomas,[7] or even normally.[14] However, the combination of a concurrently increased gallium uptake by orbits, parotids, and lungs is a frequent phenomenon in sarcoidosis and has been considered characteristic of it.[1 3-5 11]

The present study was designed to evaluate the ^{67}Ga uptake in the orbito-parotid areas in newly detected and chronic sarcoidosis patients with clinical ophthalmic sarcoid findings. Quantitation of the intensity of ^{67}Ga uptake has been based on visual inspection of the images in most studies.[1-5] Our method quantitated the intensity of gallium uptake over the orbital and parotid areas by a computer; this improved the accuracy of the evaluations and the comparability of the findings.

All but one patient in the newly detected group and all the chronic patients had one or more clinical ophthalmic sarcoid findings and 81% of all patients had a positive conjunctival biopsy. Gallium images

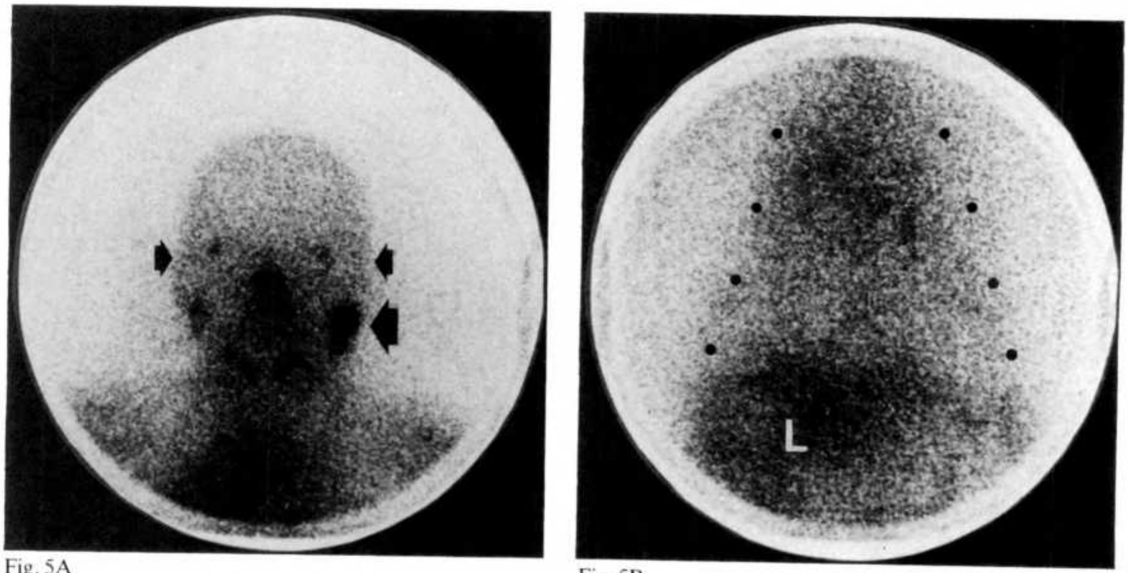

Fig. 5A

Fig. 5B

Fig. 5 *Case 3. Chronic sarcoidosis. Gallium scan showing an increased* ^{67}*Ga activity* (A) *over the orbits (157%) and left parotid (208%) (arrows) (right parotid resected), but not* (B) *in the lungs (grade 0), in a 52-year-old female with pulmonary and subclinical uveal sarcoidosis. Thoracic contours are marked with dots. L=liver.*

showed a highly significantly heavier uptake over the orbits in the newly detected patients and a significantly heavier parotid uptake of both the newly detected and chronic patients compared with the corresponding uptake in the controls. In addition all recently detected patients and two-fifths of the chronic patients showed an increased lung activity.

Bronchoalveolar lavage analyses have shown that in active pulmonary sarcoidosis ^{67}Ga is taken up by activated alveolar macrophages constituting a state of 'high intensity alveolitis', often with an increased number of activated T lymphocytes.[2] It is probable that the increased ^{67}Ga accumulation over the orbits and parotids in sarcoidosis is due to an increased density of activated macrophages in these areas, being especially prominent in the newly detected untreated cases.

Because of selection of the cases it cannot be said how often an increased ^{67}Ga uptake in the orbital and parotid areas occurs in sarcoidosis patients. Koegh and associates[2] have shown that in pulmonary sarcoidosis a state of low intensity alveolitis which includes, for example, a negative ^{67}Ga image of the lung areas (normal lung uptake) is four times more prevalent than a state of high intensity alveolitis with a positive lung image (increased lung uptake). The high intensity alveolitis in their patients was often followed by a deterioration of the lung functions. They also showed that alveolitis could be unstable and often reverted from a high intensity state to a low intensity state and, more seldom, also vice versa. The decrease of ^{67}Ga activity over the orbits, parotids, and lungs in our patient no. 2 and an increase of the lung uptake in patient no. 3 (Figs. 5 and 6) are examples of such a reversion. In patient no. 2 recovery of lacrimal secretion was seen together with a decrease in ^{67}Ga uptake over the orbits and parotids. And, further, patient no. 3 showed reactivation of uveitis with iris granulomas in association of an increased lung uptake.

The lacrimal gland, a gland comparable to the parotid in its structure and function, is possibly the main locus responsible for the ^{67}Ga uptake over the orbits in sarcoidosis. Our study suggests that the lymphoproliferative tissues of the conjunctivae and possibly also the intraocular tissues can be a site of activated cell elements to be seen in gallium imaging.

In conclusion we suggest that an increased ^{67}Ga uptake over the orbits and parotids in sarcoidosis probably indicates activation of immune effector cells in these areas, and clinical sarcoid involvement, often asymptomatic, may be revealed on ophthalmic examination. On the other hand, in chronic sarcoidosis a negative gallium image or only a slightly increased ^{67}Ga uptake over the orbits or parotids does not exclude clinical sarcoid ocular disease or granulomatous change in conjunctival specimens.

Gallium findings support the results of ophthalmological examinations[15,16] and of sialographic studies[17] and indicate that in sarcoidosis the lacrimal glands, conjunctivae, and parotid glands are affected

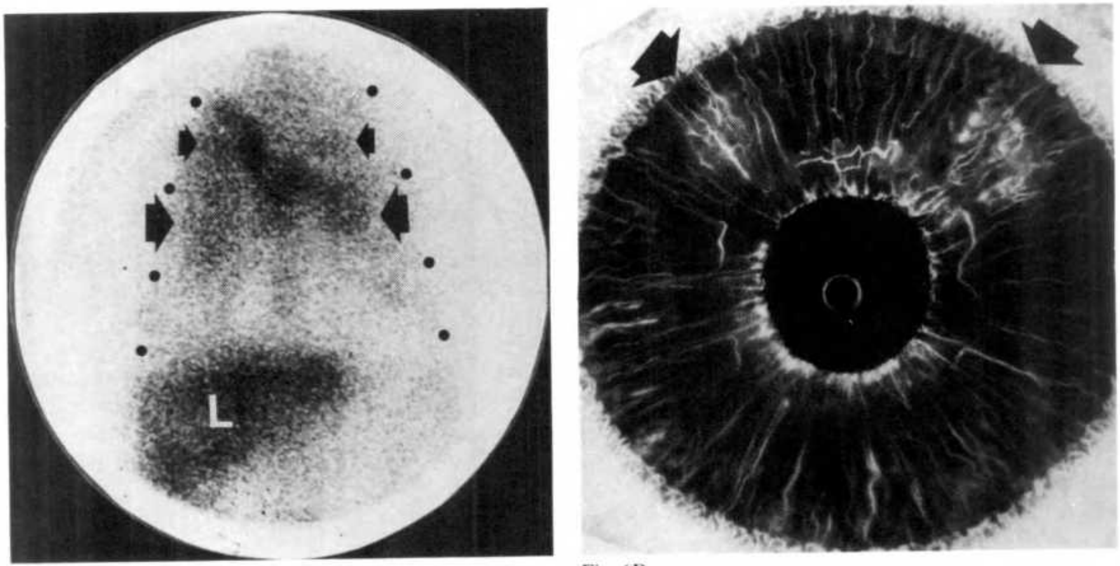

Fig. 6A

Fig. 6B

Fig. 6 *Case 3. Eight months after the phase shown in Fig. 5, soon after discontinuing prednisolone therapy an increased ^{67}Ga uptake was measured* (A) *in the lungs (grade 3) (arrows). Thoracic contours are marked with dots. L = liver. The uptake over the orbits and parotids was unchanged, although uveitis became reactivated and a* (B) *fluorescein iris angiogram showed sarcoid nodules in the left iris (arrows).*

more often than is suspected on the basis of ocular and parotid symptoms. Moreover, Heerfordt's disease, earlier regarded as a rare manifestation of sarcoidosis,[18,19] has been brought to a new focus by the gallium examinations.

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Hard contact lens migration into the upper lid: an unexpected lid lump

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SUMMARY Contact lens migration into the upper lid is a rare complication of wearing a hard contact lens. We present a case in which the only complaint was the cosmetically unacceptable appearance of a lump in the upper lid. The 76-month duration of the lesion is, we believe, the longest so far described. The histology and possible natural history of the cyst are also discussed.

A tumour of the upper lid is a rare but well described complication of hard contact lens wear. There have been 16 cases with similar features since the first report by Green[1] in 1963. We present a further case with several interesting aspects regarding the duration of the mass and histology of the cyst, which was removed virtually intact.

Case history

A 44-year-old woman was referred to the Department of Ophthalmology at the University Hospital of Wales in August 1985 with a five-year history of a non-tender, slowly enlarging swelling of her right upper lid which was becoming cosmetically unacceptable. Her general health was good and there was no history of trauma. She denied any previous ocular problems, in particular, no episodes of conjunctivitis. Interestingly, her referral to the ophthalmologists accompanied a referral to the dermatologists for an assessment of three nodules on her forehead. These were subsequently diagnosed as benign melanocytic naevi. The patient had worn contact lenses since 1968 to correct her myopia of, right, −3·0 dioptres, and, left, −3·5 dioptres. She had worn hard contact lenses up to October 1979, when she had changed to gas permeable lenses.

Examination revealed corrected visual acuity of 6/6 right and left. There was a 2 cm diameter, freely mobile, moderately firm mass in the upper medial aspect of the right upper lid, well above the tarsal plate. The mass was not tender, not fixed to skin, and did not appear to extend into the orbit. In February 1986 the cyst was excised under local anaesthesia. The lid was singly everted during infiltration with local anaesthetic, but no mass was seen. An approach was made via a curved horizontal incision 4 mm below the eyebrow. A pale yellow cystic mass was identified. Dissection from surrounding tissue proved fairly easy, apart from the inferoposterior aspect, which eventually had to be cut, resulting in the release of a small amount of purulent material, which yielded no growth on culture. Quite early on in the procedure a solid rim was noted within the translucent cyst and identified as a contact lens. The cyst was then removed virtually intact, and a probe passed through the small dehiscence left by cutting the inferior wall of the cyst passed freely into the superior fornix. The wound was closed in layers, and an examination of the lens revealed it to be an intact hard lens of strength −3·5 dioptres.

HISTOLOGY

Macroscopically the tumour consisted of a hard contact lens enclosed in a thin walled cyst measuring 1×1×0·2 cm (Fig. 1). Microscopically the cyst was lined by an epithelium of low cuboidal type which in places was several cells thick (Fig. 2), the more superficial cells being polygonal in shape. Scattered mucous secreting goblet cells were present (Fig. 3), consistent with a conjunctival epithelium origin. Elsewhere the lining was that of a stratified squamous epithelium (Fig. 4), with evidence of keratinisation in some parts. This appearance may reflect metaplastic change in conjunctival epithelium or could imply the inclusion of corneal epithelium, which might have adhered to the contact lens during its upward migration in the cyst wall.

Correspondence to Mr D Jones.

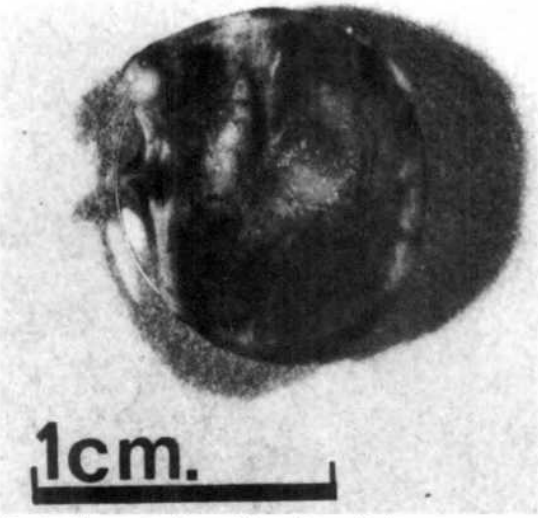

Fig. 1 *The contact lens within a thin walled cyst.*

Underlying the epithelium was a loose connective tissue containing areas of recent haemorrhage and a few lymphocyte-like cells, but there was no evidence of giant cells, or indeed of any significant inflammatory cell component. There was similarly no evidence of an excess of fibrous tissue round the cyst wall.

Discussion

Up to August 1982 there had been 16[2,3] reports of hard contact lenses being embedded in the tissues in the upper lid and fornix. This phenomenon appears to be twice as common in females as males, possibly reflecting the difference in prevalence of contact lens wear.[2] As in the previous cases of long elapses between lens loss and removal from the lid (56 months[3] and 69 months[4]), mucopurulent discharge was not a feature. However, in cases of shorter duration a chronic conjunctivitis has pointed to the true nature of the lesion.[1,5,6]

Our patient changed from hard to gas permeable lenses in October 1979. It is likely therefore that the hard lens found in the cyst had been present for at least 76 months by the time of its removal. It is probable that the duration is even longer than this,

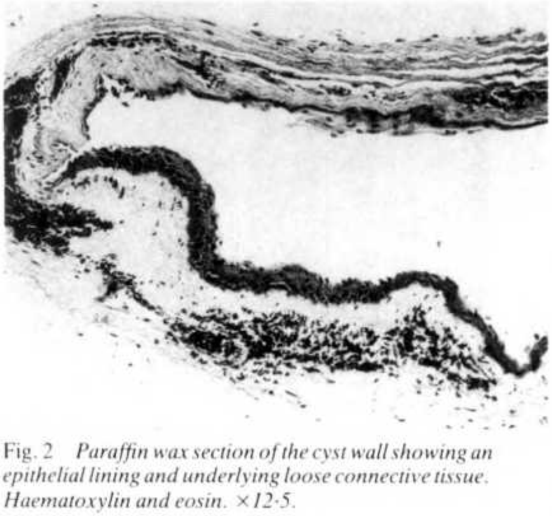

Fig. 2 *Paraffin wax section of the cyst wall showing an epithelial lining and underlying loose connective tissue. Haematoxylin and eosin. ×12·5.*

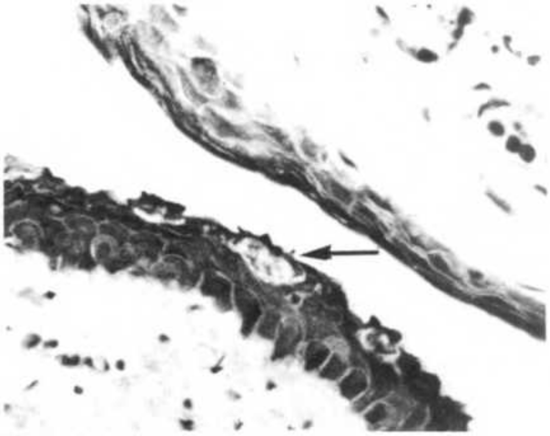

Fig. 3 *Paraffin wax section of the cyst wall showing epithelium of conjunctival type containing goblet cells (arrow). Haematoxylin and eosin. ×70.*

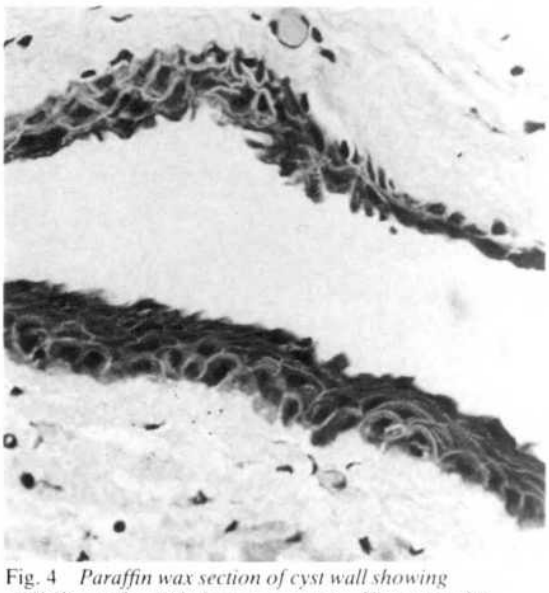

Fig. 4 *Paraffin wax section of cyst wall showing epithelium of stratified squamous type. Haematoxylin and eosin. ×77.*

since the patient was unable to recall the exact date of loss, despite admitting retrospectively to several such occurrences. We believe that the above case represents the longest duration of a contact lens 'cyst' so far described.

The quiet nature of the lesion, with no symptoms other than the presence of a lump, together with the absence of any gross inflammatory cell reaction, bears witness to the extremely inert nature of polymethylmethacrylate, from which hard contact lenses are made.

Histopathological details have been reported only in six previous cases,[1-3,7,8] one of which had a similarly non-inflammatory picture.[7] Of the others, one had a granulomatous reaction without giant cells,[3] and one other a chronic granulomatous tissue with structures suggestive of giant cells.[2] The remaining three reports mention granulation tissue but give no details. Significantly, three of the five patients with granulomatous change had symptoms, including irritation and a mucopurulent discharge.

Michaels and Zugsmith[9] postulate that it is the action of the lid on the upwardly displaced contact lens which results in local abscess formation. Rupture of the abscess then allows insinuation of the lens by erosion of the lid tissue by its edge, the entrance eventually being sealed by granulation tissue. The absence of significant inflammatory changes in our case may reflect the extremely long duration of the lesion. However, the complete lack of any irritative symptoms or discharge in this and several other cases opens to the question the theory of local abscess formation in the natural history of this condition. Possibly lid action alone may induce invagination and subsequent encysting of these very inert lenses, with no granulation tissue formation.

Finally, many authors have emphasised the need for double eversion of the lid in the examination of patients with upper lid masses and also before dispensing a new contact lens after losing an old one.[1-10] Like others we found single eversion remarkably unhelpful, and it must be pointed out that not all patients are tolerant of eversion with a Desmarres retractor in the outpatient department. In view of its rarity this condition may well remain one in which serendipity plays a large part in diagnosis.

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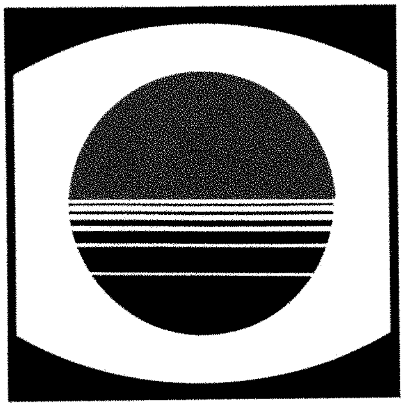

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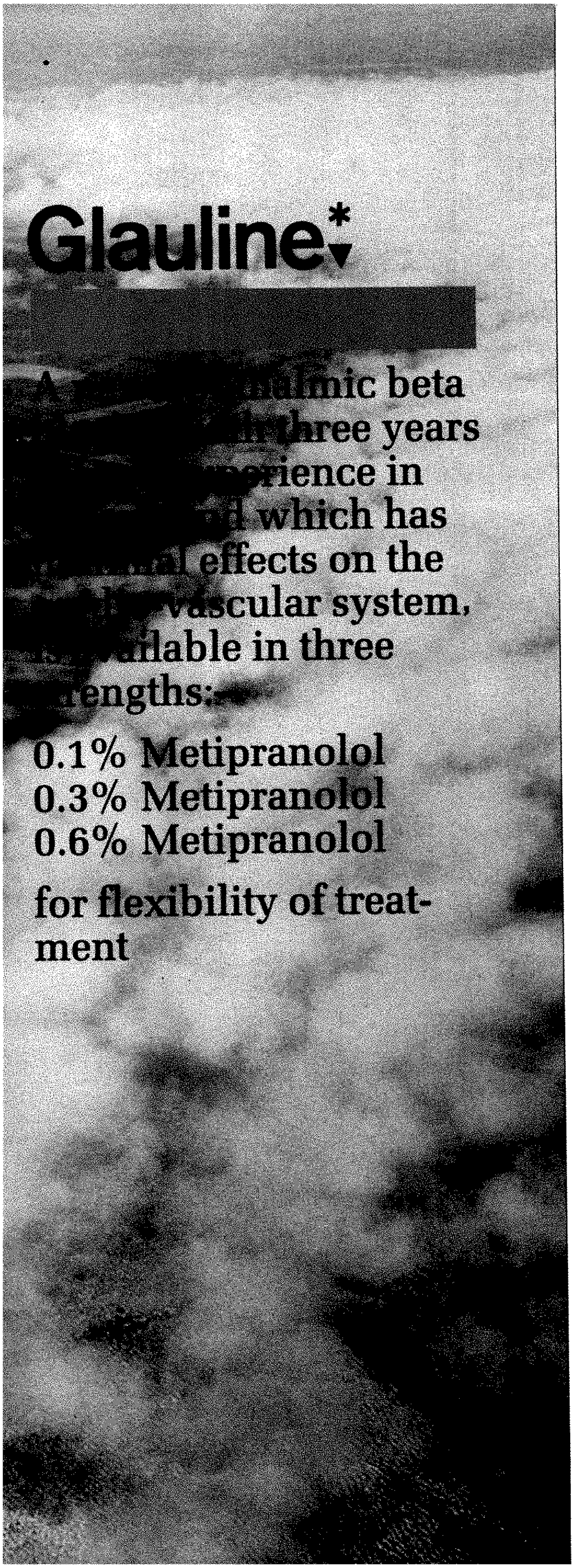

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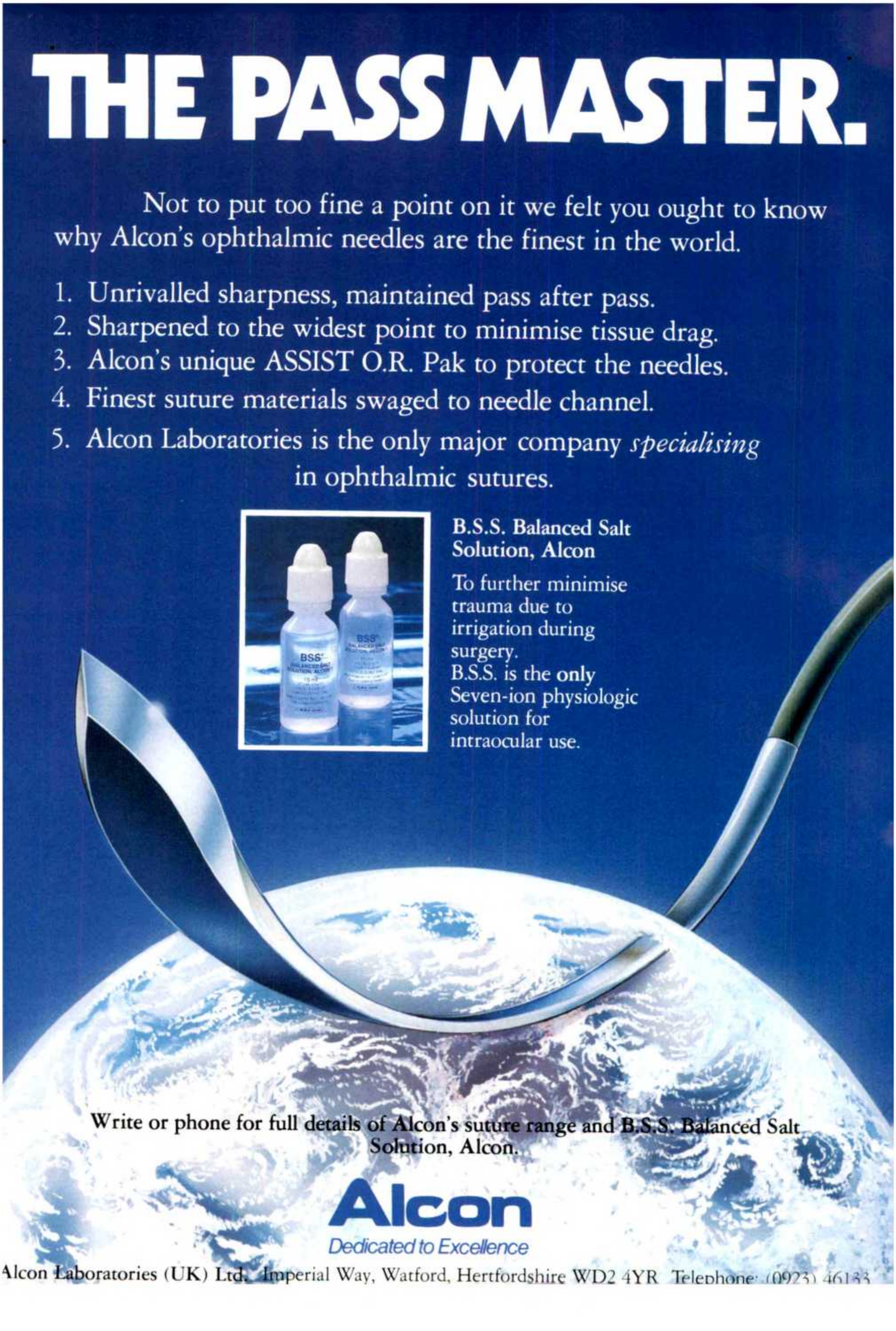

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Trachoma grading: observer trials conducted in southern Malawi

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SUMMARY A variety of grading schemes have been proposed for the clinical classification of inflammatory trachoma. During a population based study of ocular disease conducted in southern Malawi we tested a simplified version of the current WHO grading scheme. Intraobserver agreement statistics were less than satisfactory for three of four graders. Interobserver agreement when compared against either a well experienced standard ophthalmologist or a consensus grade improved over time for two of the three graders. However, initial agreement for all three graders was only fair to moderate. Previous studies of trachoma grading schemes support these unsatisfactory results. A new system of classification is needed that is both accurate and reliable in a field setting.

In regions of the world where trachoma is endemic it is a chronic, progressive disease with two overlapping phases. The inflammatory phase, indicative of active infection with ongoing transmission is found most often in children under the age of 10 years. The cicatricial phase, a consequence of chronic granulomatous inflammation, begins in childhood but does not usually become severe until later in adult life. The severity of scarring, and risk of subsequent blindness, is a function of the intensity and duration of the previous inflammatory phase. As such, the relative degree or severity of inflammation in a community is considered to be an excellent predictor of future risk of blindness in a population.

Many grading schemes have been devised over the last 50 years more accurately to classify persons or communities with varying severity of trachomatous inflammation. These have grown increasingly complex, using up to 22 signs for each eye with each sign scored from 0 to 3.[1] Even the current WHO recommended grading system uses eight signs scored from 0 to 3.[2] There are few published data on the reproducibility of these grading schemes between different observers or even between the same observer at different times.

During the course of a population-based survey of ocular disease conducted in the Lower Shire River Valley of Malawi we had the opportunity of examining intra- and interobserver reliability in the grading of trachomatous inflammation.

Material and methods

The population for the study came from a population-based prevalence survey of trachoma and other ocular diseases carried out in southern Malawi in the autumn of 1983. These studies took place in three villages adjacent to survey villages in the Lower Shire River Valley. A detailed description of the methods used in that investigation have been published elsewhere.[3] The three graders were fully qualified ophthalmologists with field experience in trachoma endemic areas. A special training programme on trachoma grading, including extensive photographic review and field examinations, was conducted by a specialist experienced in field studies of trachoma (HRT).

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Three observer trials were conducted:

Study I. In study I 20 eyes of 10 children and 60 eyes of 30 adults were graded twice by each of the three graders and the specialist. Both children and adults were assigned study numbers and seen by each ophthalmologist in a different order. The order of the subjects was then changed for the second round of grading. The most experienced ophthalmologist in trachoma grading (HRT) served as a standard against which the other three graders were compared. The analysis for the study focused on both intra- and interobserver agreement.

Study II. Approximately two weeks after study I was concluded 50 eyes of 25 children were examined independently by each of the three graders. All three graders then examined the children jointly to come to a consensus grade for each child. Five children were unavailable for the consensus examination; however, all five were given the same grade by all three observers during the initial grading round. Only interobserver agreement was calculated for this study.

Study III. Three weeks after the conclusion of study II another 40 eyes of 20 children were examined by the three graders using the same methodology as in study II. Again only interobserver agreement was analysed.

METHODS OF EXAMINATION

Examinations were conducted in the open air in full sunlight with 2·5 × magnifying loupes. The upper lid of each eye was everted and the inflammatory response was graded and recorded appropriately. The grading scheme used for these trials was a simplification of the current WHO classification scheme. Table 1 compares this system with the existing WHO system. The new scheme did not require the separate grading of follicular. and papillary response but maintained the WHO definitions for the categories that were retained. This system was considered to be easier to use in the field while disease was still classified into categories that had clinical and epidemiological relevance. The agreement analysis was conducted only for inflammatory trachoma. Cicatricial trachoma was not analysed because the field study focused primarily on young children, and the marginal distribution of scarring severity was overwhelmingly 'absent' or 'mild'.

Table 1 *Classification schemes for inflammatory trachoma*

Grade	*WHO scheme*	*Current scheme*
Absent	Five or fewer follicles in the entire tarsal conjunctiva	Same
Mild	More than five follicles in the entire tarsal conjunctiva, but less than five in zone 3	Same
Moderate	Five or more follicles in each of the three zones	Five or more follicles in zone 3
Severe	Conjunctiva thickened and opaque, normal vessels on the tarsus are hidden over more than half of the surface due to papillary hypertrophy and infiltration	Conjunctiva thickened and opaque, normal vessels on the tarsus are completely hidden due to papillary hypertrophy and infiltration

The kappa statistic was used in the analysis for both intra- and interobserver reliability.[4] Percentage agreement is an inappropriate measure of agreement in studies of this sort, because it does not correct for the amount of agreement expected from chance alone. When one category tends to be the most commonly occurring grade, percentage agreement is deceptively high. Kappa is a chance corrected measure of agreement that ranges between +1 (complete agreement) and −1 (complete disagreement). Values greater than 0 indicate agreement greater than expected by chance. Kappa statistics above 0·7–0·75 are considered by most authorities to indicate good agreement.[5] Where all types of disagreement are not the same, the standard kappa statistic can be somewhat conservative. For example, the disagreement between two observers when one observer grades inflammatory trachoma as mild and the other grades it as moderate is less than if the second observer graded it as severe. We therefore chose to use the weighted kappa statistic which permits an assignment of weights to differing levels of agreement. The weights we used are shown in Table 2. Complete disagreement was defined in the present situation when one observer reported no inflammation while another reported severe. Each less severe disagreement was then weighted more heavily in a linear fashion with complete agreement (none-none, mild-mild, etc.) given full weight. All analyses were conducted by person (not by eye) using the severity of the worst eye as the measure of inflammation.

Results

The prevalence rates of inflammatory trachoma are

Table 2 *Cell weights used for estimation of weighted kappa statistics*

Inflammatory grade	*Inflammatory grade*			
	Normal	*Mild*	*Moderate*	*Severe*
Normal	1	0·67	0·33	0
Mild	0·67	1	0·67	0·33
Moderate	0·33	0·67	1	0·67
Severe	0	0·33	0·67	1

Table 3 *Prevalence of inflammatory trachoma by person and eye*

Grade	*Study I**		*Study II†*		*Study III†*	
	Person	*Eye*	*Person*	*Eye*	*Person*	*Eye*
Normal	27 (67·5%)	56 (70·0%)	11 (44·0%)	23 (46·0%)	1 (5·0%)	2 (5·0%)
Mild	10 (25·0%)	18 (22·5%)	7 (28·0%)	14 (28·0%)	1 (5·0%)	2 (5·0%)
Moderate	2 (5·0%)	4 (5·0%)	7 (28·0%)	13 (26·0%)	10 (50·0%)	20 (50·0%)
Severe	1 (2·5%)	2 (2·5%)	0 (0·0%)	0 (0·0%)	8 (40·0%)	16 (40·0%)
Total	40 (100·0%)	80 (100·0%)	25 (100·0%)	50 (100·0%)	20 (100·0%)	40 (100·0%)

*Based on the grade of the standard ophthalmologist. †Based on the consensus of the graders.

presented in Table 3. There was very little difference in prevalence when examined by eye or by person within any one study. Study III had higher rates and more severe disease than studies I and II. This agrees with anecdotal observations made in these three locations during the conduct of the observer trials.

The analysis of intraobserver reliability examined in study I is presented in Table 4. The most consistent observer was the standard, with a kappa of 0·92; the graders ranged from 0·50 to 0·70. These kappa statistics are in the low to moderate range except for the standard, who showed excellent internal consistency.

Results for interobserver agreement are shown in Table 5. Graders 1 and 2 show a consistent increase in agreement over time; both were in the 'acceptable agreement' range by the time of study III. Grader 3 had the highest agreement in studies I and II, but fell off sharply in study III. This may reflect diagnostic drift or the small sample size. In an effort to describe the agreement based on all the data, a weighted average kappa was calculated for each examiner. These overall kappas are 0·65, 0·62, and 0·62 for graders 1, 2, and 3 respectively. While there is no basic difference among the graders, they still show agreement that is less than the acceptable range.

Discussion

All epidemiological studies are subject to measurement variability, whether they involve clinical observations, laboratory analyses, or interview based responses. Two main sources of variation in data such as these are: (*a*) sampling variability, which, if no bias is inherent in the data, can be estimated by standard statistical techniques; and (*b*) variability within and between observers. The magnitude of the latter effect is estimable only from studies undertaken specifically to evaluate it. Even then, drift in measurement may occur over time, leading to increasing unreliability in spite of earlier documentation that agreement was adequate. Standardisation of equipment, techniques, and lighting conditions can reduce this type of variability considerably. However, even when these conditions are met, the classification scheme must clearly define categories of severity.

Table 4 *Intraobserver reliability for inflammatory trachoma by person*

Graders	*Weighted kappa*	*95% CI*
1	0·70	0·47–0·93
2	0·55	0·26–0·85
3	0·66	0·41–0·92
Standard	0·92	0·80–1·00

CI=confidence interval.

Little work has been done to examine this issue in the various grading schemes for inflammatory trachoma. What studies have been done indicate that agreement is often less than satisfactory. Assaad and Maxwell-Lyons reported on interobserver trials for 574 persons examined in Taiwan[6] using a modification of the MacCallan classification. They found that, when two highly experienced ophthalmologists were compared, the percentage agreement was 68·3%. When we adjusted their findings for expected agreement, however, the weighted kappa was only 0·37 (95% confidence interval: 0·29, 0·46). Kupka and coworkers also used the same classification system for their work in Morocco.[7] They examined 100 adults and 100 school children using two graders. The

Table 5 *Interobserver agreement for inflammatory trachoma by person*

	Grader	*Weighted kappa*	*95% CI*
Study I*	1	0·58	0·31, 0·85
	2	0·51	0·30, 0·71
	3	0·64	0·38, 0·90
Study II†	1	0·64	0·41, 0·87
	2	0·61	0·41, 0·81
	3	0·71	0·51, 0·92
Study III†	1	0·80	0·56, 1·00
	2	0·86	0·67, 1·00
	3	0·47	0·11, 0·84

*Standard for comparison was the standard ophthalmologist.
†Standard for comparison was the consensus of the three graders.

school children were examined twice independently by each observer in order to estimate intraobserver variation. The interobserver percentage agreement was 53%, while the intraobserver percentage agreements were 67% and 64%. Weighted kappa statistics that we computed from their published data support these poor results. The interobserver kappa was 0·47 (95% CI: 0·36, 0·58) and the intraobserver kappas were 0·63 (95% CI: 0·49, 0·78) and 0·48 (95% CI: 0·33, 0·63). Dawson and coworkers using three observers examined 31 children in a treatment trial among American Indian children in Utah.[8] They did not report direct comparisons of observer grading, but found differential treatment effects when different observers were used. In another small treatment study Dawson and coworkers used two observers to compare the frequency of active versus inactive trachoma among 27 children.[9] The percentage agreement was 67%. With their data the kappa was 0·28 (95% CI: −0·03, 0·60). Observer trials were also conducted by the Royal Australian College of Ophthalmologists[10] during their National Trachoma and Eye Health Program. Three graders were compared for both intra- and interobserver agreement by means of photographs and a grading scheme indicating presence or absence of active follicular disease. Our calculations on their published data show that intraobserver agreement was good, with kappas ranging from 0·72 to 0·94. Interobserver agreement was not as good, however. The kappa was 0·54 (95% CI: 0·45, 0·63) using the extension of the method for more than two observers.[4] The most recent work in this area has been done by Brilliant and others in the Nepal Blindness Survey.[11] They conducted a rigorously designed assessment of observer variation for a variety of ocular conditions. Their trachoma grading system was a modification of the currently recommended WHO classification. Results revealed poor interobserver agreement for active inflammatory disease. Kappas for varying intensity levels ranged from 0·31 to 0·51 depending on whether inflammation was graded on a 4-point or 2-point scale. The kappa for overall intensity grade in the worst eye was 0·36.

Despite using a simplified version of the current WHO classification scheme and well trained and experienced ophthalmologists, our results are little better than those previously reported. While we noted that graders 1 and 2 improved to an acceptable level over time, grader 3 showed significant diagnostic drift, which emphasises the importance of restandardising clinical observers during the course of a protracted observation period.

The present study confirms that the current system for grading inflammation is inadequate. A new system of classification is needed if accurate and reproducible clinical observations are to be obtained for use in epidemiological studies of trachoma.

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Retinal break formation following contrecoup trauma: case report

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SUMMARY A previously healthy 38-year-old woman was involved in a road traffic accident resulting in severe commotio retinae. Subsequently extramacular retinal dissolution was noted (not previously described). The patient was treated by closed intraocular microsurgery with a successful anatomical and functional result.

Retinal dissolution at the site of impact is recognised as a complication of coup injuries. Contrecoup injuries have been reported only as leading to retinal hole formation at the macula. This case demonstrates extramacular retinal dissolution following a contrecoup injury (commotio retinae). Internal surgical repair was carried out with a successful result.

Case report

In June 1984 a previously healthy 38-year-old woman was a front seat passenger in a road traffic accident. She suffered right forehead and upper eyelid lacerations but no skull fracture. She was conscious and orientated and complained of blurred vision in the right eye. As her lacerations were repaired under general anaesthesia her eye was also examined.

Her pupil was noted to be slightly dilated but regular. The fundus showed extensive posterior pole commotio retinae extending just above the superotemporal arcade, 2 disc diameters nasal to the disc and inferiorly to the equator. No retinal breaks were apparent.

Postoperatively she developed diplopia secondary to a right sixth nerve palsy. This rapidly resolved, with no permanent clinical abduction deficit. After seven days her visual acuity was 6/9 and her commotio retinae rapidly resolving.

She was discharged and seen for review elsewhere. She was referred back in April 1985 having noticed in the previous months floaters and a superior, irregularly shaped scotoma slowly encroaching on fixation.

Fundus examination showed two large and one small closely related breaks approximately two disc diameters below the inferotemporal arcade (Fig. 1). The edges were shallowly elevated, and subretinal fluid extended under the inferotemporal arcade. Her visual acuity was 6/6 and her macula attached. There was no apparent posterior vitreous detachment, and preoperative ultrasound could not demonstrate the posterior vitreous face.

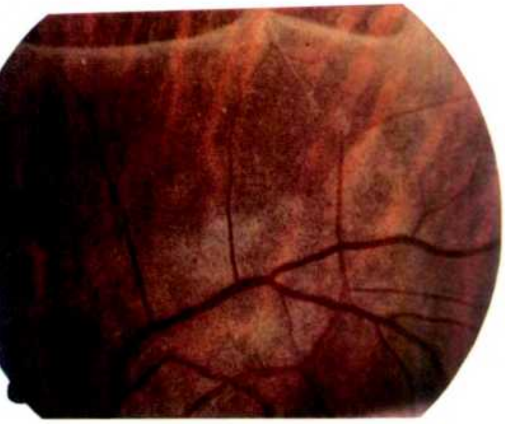

Fig. 1 *Preoperative fundal view showing the relation between the upper part of the retinal breaks and the inferotemporal arcade, with subretinal fluid extending under the inferotemporal arcade. (The third small break is not shown in this view.)*

Because of the location and size of the holes an internal repair was carried out, consisting of ocutome vitrectomy, internal tamponade with an air/fluid exchange, and, in the absence of endophotocoagulation, external cryotherapy. The postbasal cortical gel remained in situ, and 360° cryotherapy was applied to the postoral retina.

Her postoperative course was uneventful. Her

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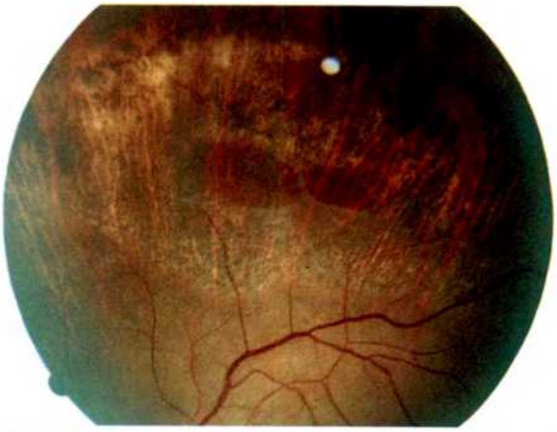

Fig. 2 *Postoperative fundal view showing full extent of retinal breaks and surrounding cryoreaction.*

visual acuity remains normal and her fundus shows a good cryoreaction below the inferotemporal arcade (Fig. 2). No peripheral breaks were visualised at the time of or subsequent to surgery.

Discussion

Large irregular retinal breaks have been recognised as a complication of blunt trauma at the point of impact.[1–4] They are often associated with choroidal rupture, retinal, vitreous, and choroidal haemorrhage, and later onset of choroidal and retinal pigment epithelium atrophy.[1,2,5] These breaks are evident soon after injury,[2,5] lead to retinal detachment, and have been attributed to acute retinal necrosis and mechanical disruption.[5,6]

Commotio retinae is a contrecoup injury[7] involving the outer retinal layers which macroscopically become opaque.[8,9] It may resolve rapidly with a corresponding increase in visual acuity.[4] It may also be associated with minor pigment epithelium disturbances, particularly at the macula, and may lead to macular hole formation.[1,2,10] This case shows large areas of dissolution in an area of the posterior pole previously noted to have commotio retinae. The time between break formation and injury is longer than that associated with breaks resulting from direct trauma, and although fluorescein angiography was not carried out there appears to be no choroidal or pigment epithelial involvement.

Large retinal breaks resulting from coup injuries are well documented, but not as a result of a countrecoup (commotio retinae) injury. The mode of injury, with the right forehead and upper eyelid involvement, and in the absence of damage to the inferior orbital margin, suggests a contrecoup injury. A small amount of traumatic mydriasis is known to be associated with contrecoup fundal changes.[1,4]

Experimental animal studies have shown commotio retinae to consist of acute photoreceptor outer segment disruption with no extracellular oedema. This is followed by immediate loss of photoreceptor cell bodies in the outer nuclear layer, the permanent outcome being loss of photoreceptor cells.[8] The final visual outcome depends on the amount of macular photoreceptor cell loss. Severe loss will lead to lamellar or full thickness hole formation because of the absence of other tissue, apart from glial processes, in this area. As extramacular areas are composed of more retinal layers, widespread photoreceptor cell loss alone should not lead to hole formation.

The cause of retinal dissolution in this case is most likely multifactorial. In addition to widespread photoreceptor cells loss there may be loss of inner retinal layers and vitreoretinal interactions leading to hole formation. 360° cryotherapy was carried out as a prophylaxis against giant tear formation as the post-basal cortical gel remained intact.[11]

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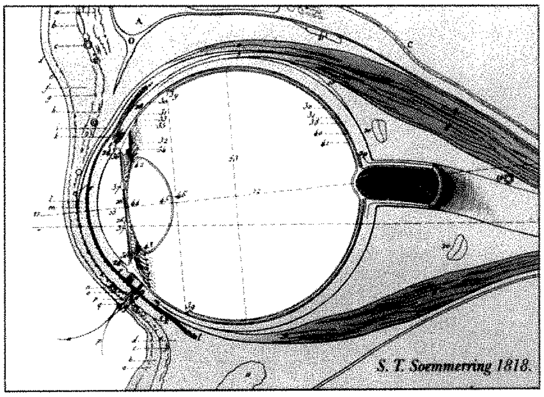

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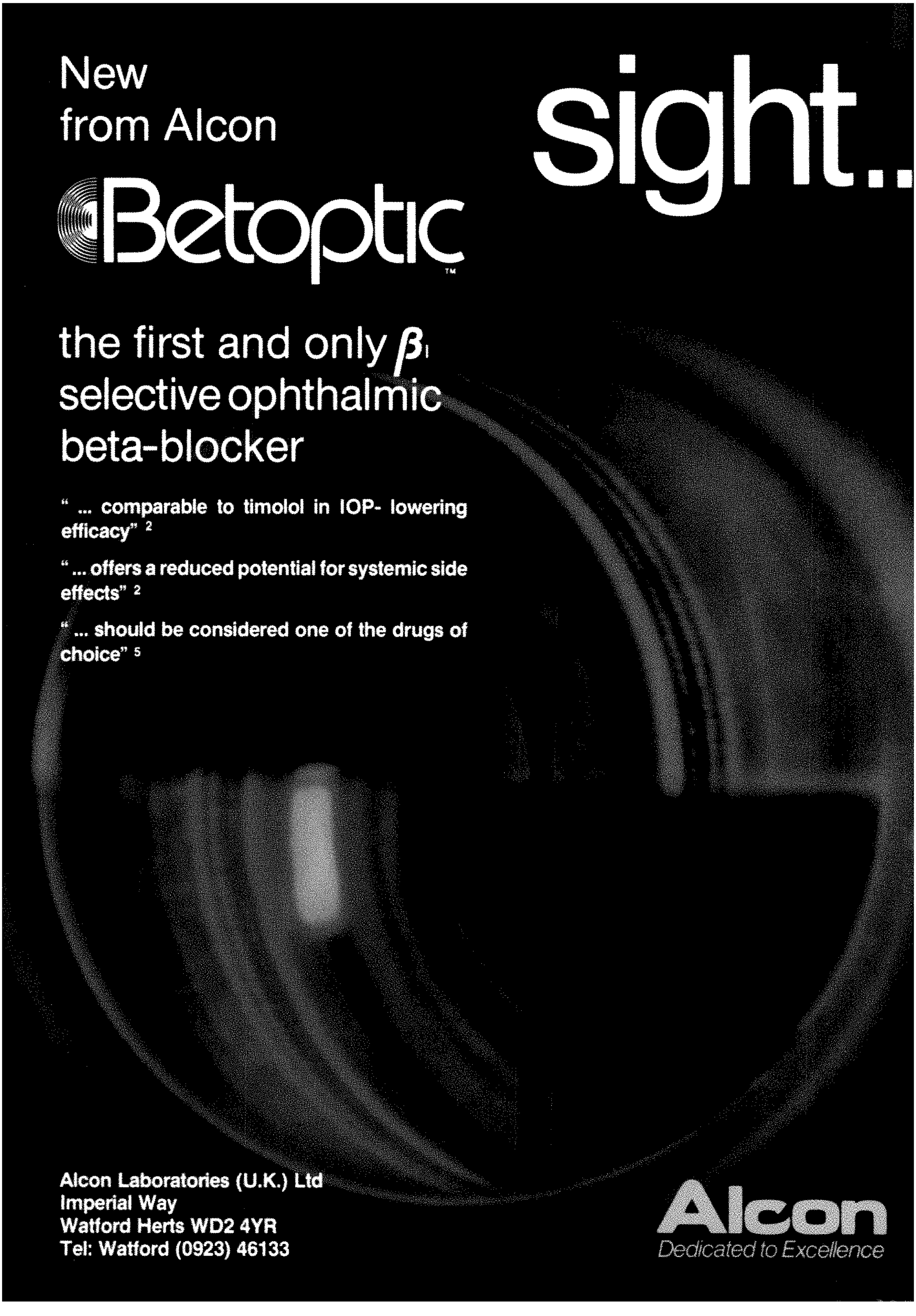

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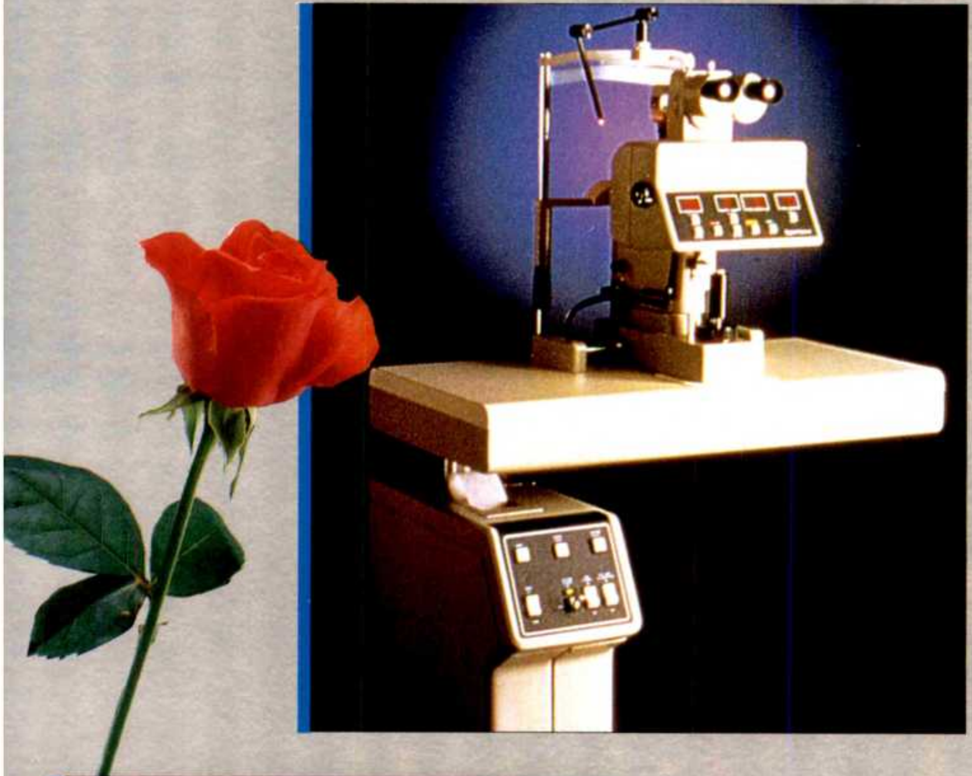

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Large unilateral medial rectus recession for the treatment of esotropia

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SUMMARY Sixteen patients with moderate angle esotropia of 30 to 35 prism dioptres were treated with a unilateral medial rectus muscle recession of 6 or 6·5 mm. Thirteen of sixteen patients (80%) were straight postoperatively or had 12 prism dioptres or less of esotropia. Three of the 16 had greater than 12 prism dioptres of esotropia, and none were exotropic. This procedure should be considered as an alternative approach in the treatment of moderate angle esotropia.

The recession of a single medial rectus muscle for the treatment of various forms of esotropia has been well described. Chamberlain reported 100 cases of unilateral medial rectus recession of 3·5 to 4 mm and concluded that it was a feasible operation for minimal non-accommodative esodeviations measuring less than 20 prism dioptres.[1] A unilateral medial rectus muscle recession of 5 mm has also been successfully used to treat small angle partially accommodative or residual esotropia.[2] In addition, high AC/A ratio has been treated with 5 and 5·5 mm single medial rectus muscle recession.[3 4]

Large (6 and 6·5 mm) unilateral medial rectus recession as a treatment for moderate angle esotropia (30 to 35 prism dioptres) has not been previously reported to our knowledge. It is the purpose of this paper to review the results of unilateral large medial rectus recessions for the treatment of moderate angle esotropia.

Subjects and methods

The records of all patients who underwent 6·0 or 6·5 mm unilateral medial rectus muscle recession at the Pediatric Ophthalmology Service of Wills Eye Hospital between July 1981 and October 1985 were reviewed. A total of 21 patients, excluding patients with Duane's retraction syndrome, underwent a single medial rectus muscle recession during this period. Sixteen patients met the criteria for inclusion in the study, which were as follows: (1) preoperative esotropia of 30 to 35 prism dioptres; (2) no previous horizontal muscle surgery; (3) full ductions and versions preoperatively; and (4) follow-up of two months or more. Deviations were measured by the Hirschberg or Krimsky methods in young children or in patients with dense amblyopia. The prism and cover tests were used when possible.

All patients underwent a 6·0 or 6·5 mm unilateral medial rectus muscle recession. The amount of recession was measured from the posterior aspect of the muscle insertion. The amblyopic eye was operated on in the 12 patients with amblyopia. A 6·0 mm recession was performed for esotropia of 30 prism dioptres and a 6·5 mm recession for 35 prism dioptres except for case 11. In this case a 6·0 mm recession was performed for a 35 prism dioptre esotropia. Because of the undercorrection it was decided that all subsequent cases of 35 prism dioptre esotropia should undergo a larger recession. Surgery was performed under general or retrobulbar anaesthesia by the Parks cul-de-sac approach. In three patients the surgical procedure was modified to an adjustable suture technique which as been previously described.[5]

Postoperative measurements are those obtained at the most recent follow-up visit. For the purpose of this study an alignment within 12 prism dioptres of straight at the most recent follow-up visit was considered a good result. The majority of patients in this study were amblyopic, and in these patients an alignment within 12 prism dioptres of straight can be considered a cosmetically acceptable postoperative result. Further, in patients with esotropia associated with impaired vision an undercorrection would be desirable because of the tendency for eventual replacement of the esotropia with secondary exotropia.[6]

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Results

Sixteen consecutive patients underwent a 6 or 6·5 mm unilateral medial rectus muscle recession. All patients had a postoperative deviation of 30 to 35 prism dioptres of esotropia, with a mean deviation of 30 prism dioptres (Table 1). Patients ranged in age from 3 to 57 years with an average age of 21·5 years. Follow-up ranged from 2 to 31 months with an average follow-up of 9·3 months. Twelve of 16 patients (75%) had decreased vision in the strabismic eye secondary to amblyopia. Three patients underwent a 6 mm recession by means of an adjustable suture; however, none of these patients required any adjustment. Therefore in these three patients the amount of recession remained at 6 mm.

For a 6 mm recession (14 patients) the mean postoperative deviation was 6·6 prism dioptres, with a range of 0 to 20 prism dioptres of esotropia. The average amount of correction for a 6 mm recession was 21 prism dioptres.

Table 1 *Summary of clinical status*

Case	*Age (yr)*	*VA*	*Preop. deviation (PD)*	*Postop. deviation (PD)*	*Medial rectus rec. (mm)*	*Follow-up (months)*
1	5	OD=20/30 OS=20/200	30	0	6	12
2	21	OD=20/20 OS=20/20	30	0	6	12
3	11	OD=20/20 OS=20/40	30	0	6	9
4	3	OD=20/100 OS=20/30	30	0	6	5
5	6	OD=20/20 OD=20/50	30	2	6	3
6	4	PD=20/20 OS=CF at 2 feet (0·6 m)	30	6	6	9
7	6	OD=20/200 OS=20/20	30	20	6	9
8	44	OD=20/20 OD=20/200	30	8	6	8
9	35	OD=20/20 OS=20/70	30	12	6	2
10	36	OD=20/20 OS=20/20	30	2	6	3
11	57	OD=20/20 OS=20/20	35	20	6	20
12	33	OD=20/20 OS=CF at 3 feet (0·9 m)	30	8	6 Adj.	31
13	46	OD=20/20 OS=20/20	30	15	6 Adj.	9
14	30	OD=20/30 OS=20/20	30	4	6 Adj.	4
15	4	OD=20/60 OS=20/30	35	10	6·5	6
16	3	OD=20/30 OS=20/80	35	6	6·5	7

OD=Right eye. OS=Left eye. CF=Counting fingers. PD=Prism dioptres. VA=Visual acuity. Adj.=Adjustable technique. Rec.=Recession.

For a 6·5 mm recession (two patients) the mean postoperative deviation was 8 prism dioptres, with a range of 6 to 10 prism dioptres of esotropia. The average amount of correction for a 6·5 mm recession was 27 prism dioptres.

Of the 16 patients treated 13 (80%) were aligned within 12 prism dioptres of straight. Of the remaining patients three were undercorrected. None of the patients were overcorrected. In addition, clinically or cosmetically significant limitation of adduction or lateral incomitance was not noted in any of the patients.

Discussion

A large recession of a single medial rectus muscle is an effective method of correction for moderate angle esotropia. In this study 75% of patients had impaired vision in the strabismic eye secondary to amblyopia. In an amblymopic eye with esotropia the standard surgical procedure is a recession of the medial rectus muscle combined with a resection of the lateral rectus muscle. The single medial rectus muscle recession, however, has a number of advantages. A single muscle recession is technically easier than performing a recession and resection in the involved eye. There is less of a tendency toward bleeding in recessions, since the tendon rather than the muscle is severed. The anaesthesia time would be shortened considerably with a single muscle recession. If reoperation for an over- or undercorrection is necessary, the lateral rectus muscle can be recessed in the case of an overcorrection or resected for an undercorrection.

Large bimedial recessions in excess of the traditional 5 mm have been well described. High rates of success have been reported with large (6 and 7 mm) bimedial recessions in patients with large angle congenital esotropia.[7-9] Critics of large medial rectus recessions have stated that a crippling of adduction may result. Beisner,[10] however, showed through mathematical analysis that a bimedial recession of 8 mm would result in a loss of only 10% torque when the eye is adducted 15°. In addition, Mittleman and Folk[11] have presented clinical evidence that a re-recession of the medial rectus 13·5 mm from the limbus is a safe and effective procedure. In the 16 patients in this study a significant limitation of adduction was not noted.

A large unilateral medial rectus muscle recession is an effective and safe method of treating moderate angle esotropia. We found the overall correction for a 6 mm recession to be 21 prism dioptres and for a 6·5 mm recession 27 prism dioptres.

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Surgical management of large angle congenital esotropia

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SUMMARY Ninety-seven patients with congenital esotropia with deviations of 50 prism dioptres or greater underwent large (6 and 7 mm) bimedial rectus recessions. The overall success rate with one operation was 83·5%. Judgment of final alignment was made at the last follow-up examination, six to 61 months (average 23·4 months) postoperatively. Large bimedial rectus recessions for congenital esotropia are an effective surgical treatment which does not significantly alter adduction.

The best surgical treatment of large angle congenital esotropia continues to be controversial. Success rates ranging from 40 to 80% have been described with a variety of surgical techniques.[1-8] Traditionally the maximum recession of the medial recti has been approximately 5 mm.[7] Several investigators have successfully corrected large angle esotropia with bimedial rectus recessions in excess of the traditional 5 mm.[9,10] Mittleman and Folk have presented favourable results following re-recession of the medial rectus 13·5 mm from the limbus for undercorrected esotropia.[11]

In a preliminary report we showed a 91% success rate with 6 or 7 mm bimedial rectus recessions in 45 congenital esotropes with deviations of 50 prism dioptres or greater.[12] Judgment of final alignment was made six weeks postoperatively, with an average follow-up of 13 months. This report presents the long term follow-up of 6 and 7 mm bimedial recessions for the treatment of large angle congenital esotropia.

Material and methods

The records of 321 patients with congenital esotropia who underwent surgery at the Pediatric Ophthalmology Service of Wills Eye Hospital between 1979 and 1985 and 136 patients from Albany Medical College between 1981 and 1985 were reviewed. Ninety-seven patients met the criteria for inclusion in this study, which were as follows: (1) constant esotropia present by 6 months of age by history and documented by one of the authors by 1 year of age; (2) preoperative deviation of 50 prism dioptres or greater; (3) alternation of fixation; (4) age of initial operation 2 years or younger; (5) no overt evidence of central nervous system abnormalities or organic eye disease; and (6) follow-up of six months or more.

Cycloplegic refraction with 1% cycloplentolate, and in some cases 1% atropine, was performed in all cases. Patients in whom the spherical equivalent was greater than +3·00 dioptres were fitted with spectacles. If the hyperopic correction reduced the esotropia to less than 50 prism dioptres, the patient was eliminated from the study.

Deviations were evaluated by the Hirschberg or Krimsky methods (base out prism in front of each eye) or by the prism and cover test when possible.

All patients underwent bimedial rectus recessions of 6 or 7 mm by the Parks cul-de-sac approach. For this study an alignment measured between orthophoria and less than 10 prism dioptres of esotropia was considered a success. For the purposes of data analysis the measurement obtained at the last follow-up visit (six months or greater) was used as the final alignment except in those patients subsequently requiring reoperation. In patients reoperated upon the alignment obtained before the second operation was used as the final result from the first operation. If a recurrent esotropia developed, full cycloplegic hyperopic correction of +1·50 dioptres or greater

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was prescribed. For these patients final ocular alignment was recorded with their spectacles.

Results

Eighty-eight patients had deviations in the range 50 to 70 prism dioptres and underwent bimedial rectus recessions of 6 mm. The remaining nine patients had deviations in excess of 70 prism dioptres and had bimedial rectus recessions of 7 mm. The average deviation in the 6 mm group was 58·2 prism dioptres of esotropia and the average for the 7 mm group was 75 prism dioptres. The ages at the initial surgery ranged from 4 months to 24 months (average 12·2 months) for the 6 mm group and 6 months to 20 months (average 9·9 months) for the 7 mm group. Refractive errors ranged from −4·75 to +4·50 dioptres (average 1·68 dioptres) for the 6 mm group, and +0·25 to +3·00 dioptres (average +1·86 dioptres) for the 7 mm group (Table 1). Follow-up ranged from six months to 61 months, average 23·3 months, for the 6 mm group, and ranged from seven months to 48 months, average 23·8 months, for the 7 mm group.

Of the 88 patients who underwent 6 mm recessions 73 (83%) had ocular alignment between orthophoria and 10 prism dioptres of esotropia at the last follow-up visit (six months or greater). Four of the 73 patients redeveloped esotropia of 15 prism dioptres or greater, which was corrected with hyperopic spectacles averaging 3·44 dioptres. The esotropia redeveloped on average 21·5 months after the initial surgery.

Thirteen patients in the 6 mm group required a second operation for esotropia at an average interval of 11·2 months after the first surgery. Five of the 13 patients were initially controlled with a hyperopic correction before the condition decompensated, requiring surgery at an average interval of 22·6 months after the first surgery. Two patients in the 6 mm group developed a consecutive exotropia at six months and 18 months following the initial surgery for esotropia. Neither patient had developed amblyopia.

Table 1 *Summary of clinical data*

	Bimedial rectus recessions	
	6 mm group	*7 mm group*
Average deviation (PD)	58·2	75
Average age (mon)	12·2	9·9
Average refraction (D)	+1·68	1·86
Success rate	83%	88·8%
Average follow-up (mon)	23·3	23·8

PD=prism dioptre. D=dioptre. Mon=months.

Eight of nine patients (88·8%) in the 7 mm group had a successful surgical result. Only one of the nine patients in this group required a second operation for esotropia at 28 months after the first surgery. One additional patient redeveloped esotropia of greater than 15 prism dioptres at 30 months following the initial surgery, which was corrected with +2·50-dioptre spectacles. None of the patients in this group developed a consecutive exotropia. Overall 83·5% of both groups combined were successfully aligned. In addition no limitation of convergence or adduction was noted in any of the patients.

Discussion

The correction of congenital esotropia has been attempted by a variety of surgical techniques. Proponents of two-muscle surgery advocate as the initial procedure either symmetrical bimedial rectus recession or monocular medial rectus recession combined with lateral rectus resection regardless of the size of the preoperative deviation.[12,13] Further surgery, either bilateral rectus resections or medial rectus recession and lateral rectus resection on the fellow eye, is performed if the patient needs additional surgery. In the past surgeons favouring bimedial rectus recessions for congenital esotropia have encountered an unacceptable incidence of undercorrections in patients with large deviations. For this reason many have turned to three- and four-muscle surgery as an initial procedure.[3,5,8,14,15]

Ing and coworkers reported a success rate for bimedial rectus recession of only 30% in 40 patients with esotropia measuring 50 prism dioptres or greater.[1] Although the authors did not specifically indicate how much medial rectus recession was performed, in 1966, when the paper was published, it would be reasonable to assume the maximum recession was 5 mm.

Helveston and colleagues reported a 72% success rate for congenital esotropia using graded bimedial rectus recession (maximum recession of 5·5 mm) with the measurement performed from the limbus, combined with recession of conjunctiva and Tenon's capsule.[4] However, the average preoperative deviation was only 38·3 prism dioptres, and assessment of final alignment was made six weeks postoperatively. More recently they described an 82% success rate using a similar recession technique with a five-month to seven-year follow-up.[6] In this study 63·9% of the patients had a preoperative esotropia of 40 prism dioptres or less.

Kushner and Morton recently reported an 84% success rate for congenital esotropia with preoperative deviations of 35 prism dioptres or greater, assessed six months postoperatively, using non-graded bimedial recessions measured from the limbus.[7] The medial recti were recessed so that the distance from the corneoscleral limbus to the recessed muscle equaled 10·5 mm. Although the average preoperative deviation was 53 prism dioptres, 35·9% of the patients had a deviation less than 50 prism dioptres with 15·4% having a deviation of 35 prism dioptres.

In 45 congenital esotropes with deviations of 50 prism dioptres or greater we reported a 91% success rate using large (6 and 7 mm) bimedial recessions. However, judgment of final alignment was made six weeks postoperatively.[12]

von Noorden and coworkers performed a monocular recess-resect operation on 50 congenital esotropes with a 42% success rate after one operation[2]; 40% of the patients had a preoperative deviation of less than 40 prism dioptres. The maximum medial rectus recession performed, although not stated in the paper published in 1972, would presumably have been 5 mm.

The alternative approach to the treatment of congenital esotropia with surgery on three or four of the horizontal rectus muscles has been reported by several investigators. Foster and coworkers described a 79% success rate with a 5·19 years' average follow-up with one operation using this approach.[3] However, 67·6% of their patients had preoperative deviations of less than 50 prism dioptres and 38·2% had 30 prism dioptres of esotropia or less. Lee and Dyer[5] reviewed 36 congenital esotropes who underwent bimedial rectus recessions and bilateral rectus resections with a 61% success rate. In their report 83·3% of the patients had preoperative deviations of 40 prism dioptres or less.

Hirsch and Scott studied 107 congenital esotropes with deviations of 50 prism dioptres or greater in which 57 had a bimedial rectus recession, two had monocular resection-recession, and 48 had three- or four-horizontal-muscle surgery.[15] The success rate for the two-muscle surgery was 37·3% compared with 64·5% for the three- or four-muscle procedure. No mention is made about how much medial rectus recession was performed.

Helveston and coworkers suggested that undercorrected esotropia or large consecutive exotropia requiring further surgery was obvious soon after the initial operation.[6] Recently Bateman and coworkers used computer based discriminant analysis to study the results of congenital esotropia surgery.[16] They discovered that the preoperative deviation, amount of medial rectus recession, and the interval between the onset of the esotropia and surgery were all statistically significant predictive variables for the surgical outcome six weeks postoperatively. In addition they found that only the postoperative deviation at six weeks was predictive of the long term deviation.

We found that for the 13 patients in the 6 mm group who required a second operation for esotropia the average interval was 11·2 months after the first surgery. Five of the 13 patients required further surgery at an average interval of 22·6 months. In addition the two patients with a consecutive exotropia developed the deviation at six months and 18 months.

Freeley and coworkers reported on a group of patients with congenital esotropia who were surgically aligned prior to 18 months of age.[17] They found that 28% of these patients later redeveloped esotropia, with an average time of onset at 14 months postoperatively. 78% of this group were corrected with hyperopic spectacles. Five patients in our study fell into this category, and the eyes were straightened with hyperopic spectacles averaging +3·25 dioptres. The esotropia redeveloped an average of 23·6 months after the initial surgery.

Hess and Calhoun were early proponents of bimedial rectus recessions in excess of the traditional 5 mm in patients with large angle esotropia.[9] They reported 30 patients ranging in age from 5 months to 12 years, with an average age of 4 years, who underwent graded bimedial rectus recessions of 6 to 8 mm. 84% of the patients in the 6 mm group (average preoperative deviation 57 prism dioptres) and 60% in the 7 mm group (average preoperative deviation 78 prism dioptres) were within 10 prism dioptres of orthophoria following the initial procedure. The one patient who had 8 mm recessions for an esotropia of 90 prism dioptres was undercorrected. Prieto-Diaz, who was also an early advocate of large bimedial rectus recessions for congenital esotropia, reported that slightly over 80% of his 85 patients had successful realignment which remained stable over a three-year follow-up period.[10]

Our overall success rate of 83·5% for the 6 mm and 7 mm groups corroborates the experience of Prieto-Diaz.[10] Although our results are similar to those of Kushner and Morton[7] and Helveston and coworkers,[6] our series included only congenital esotropes of 50 prism dioptres.

We have found that bimedial rectus recessions of 6 and 7 mm, although larger than the conventional maximum, do not result in limitation of convergence or adduction. Avoiding surgery on additional muscles saves anaesthesia time and minimises potential surgical complications. Our overall success rate of 83·5% suggests that patients with large angle congenital esotropia can be effectively aligned with graded two-muscle surgery and that this postoperative alignment is generally stable over an extended follow-up period. We therefore recommend large bimedial rectus recessions as the initial surgical management for this condition, recessing each medial rectus 6 mm for 50 to 70 prism dioptres of esotropia and 7 mm for greater than 70 prism dioptres.

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T lymphocytes of the normal human cornea

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SUMMARY Lymphocytes in the periphery of the normal human cornea are identified as being only T lymphocytes by immunhistochemical methods. OKT-4 positive cells (T-helper/inducer lymphocytes) and OKT-8 positive cells (T-suppressor/cytotoxic lymphocytes) are found in similar numbers in most of the corneas examined. OKT-4 positive cells in the cornea present a risk of transferring HTLV-III (HIV) by corneal grafting.

Lymphocytes are present in the epithelium and the stroma of the normal human cornea even in the absence of any pathological process.[1] They occur sporadically in the periphery and in low numbers in more central parts of the cornea.

Lymphocytes can be specified into their subtypes by means of monoclonal antibodies against different epitopes of glycoprotein nature on the cells. Meanwhile an increasing number of different clones and antibodies is produced reacting with the same subtype of leucocytes. Recently the Committee on Human Leucocyte Differentiation Antigens proposed a new nomenclature system using the so-called cluster designation (CD) to characterise the cells and their antigens.[2] For instance, T-helper/inducer cells are characterised by the cluster CD4, corresponding to a variety of antibodies like T4, Leu3a, or 91D6. The cytotoxic/suppressor subset of T lymphocytes in this nomenclature is characterised by the cluster designation CD8 corresponding to a number of monoclonal antibodies like Leu2a, TB, M236, etc.[2] Some of these antibodies are produced commercially, such as OKT-4 (T-helper/inducer cells), OKT-8 (suppressor/cytotoxic T cells), and OKT-3, OKT-11 (all T cells, T cells forming E-rosettes.)[3,4] Even B lymphocytes can be identified by an antibody like OKB-7.[5,6]

These antibodies became an important tool for analysing immune mechanisms under normal and pathological conditions. One of the most recent instances is the aquired immune deficiency syndrome (AIDS), a disease caused by the human T-lymphotropic virus type III (HTLV-III, HIV), which injures the T-helper/inducer cells and finally leads to opportunistic infections and neoplasms. Meanwhile it seems to be proved that the CD4 antigen is an essential and specific component of the receptor for the HTLV-III.[7-10]

Material and methods

We examined 20 normal corneas which had been obtained as fresh donor material for keratoplasty. A specimen of the corneal periphery was excised and cryostat sections cut at −20°C. The sections were allowed to dry at room temperature and were fixed in acetone for 10 minutes.

Histochemical staining of lymphocytes was performed by immunoperoxidase technique: (1) pretreatment of tissue with normal serum; (2) incubation with the primary mouse monoclonal antibody; (3) incubation with antimouse immunoglobulin (linking reagent); (4) incubation with peroxidase labelled mouse IgG; (5) addition of the substrate reagent (amino-ethylcarbazole and hydrogenperoxide). After each step the specimens were washed several times with phosphate buffered saline.

As primary antibody we used the OKB-7 antibody as reagent for B lymphocytes and OKT-11 for T cells in general. T-helper/inducer cells were identified by the OKT-4 antibody and the T-suppressor/cytotoxic subset by the OKT-8 antibody.

Results

Specimens of the periphery of 20 different corneas were examined, and lymphocytes were identified by immunohistochemical staining in 16 samples. Using the OKB-7 antibody we could detect no B lymphocytes in the cornea. Positive controls for the binding of B lymphocytes to the OKB-7 antibody were performed with fresh tissue obtained from tonsil-

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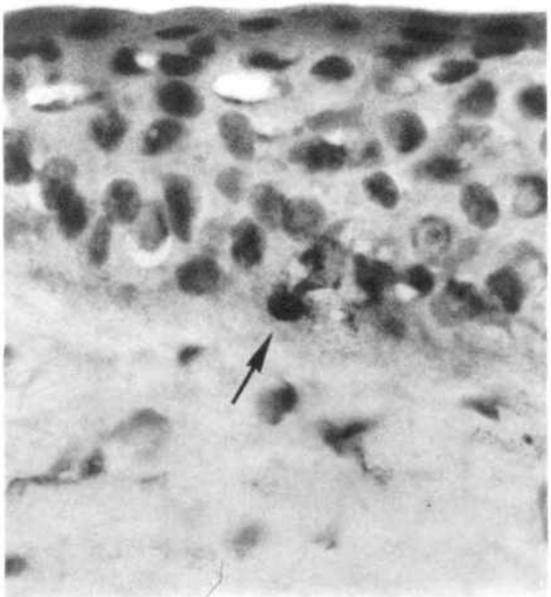

Fig. 1 *Immunoperoxidase staining of a T4 lymphocyte in a normal human cornea.*

lectomy. The sections were processed in the same way as described for the corneal specimens. All lymphocytes were identified as T cells (Fig. 1). False positive results due to artefacts could be excluded by using murine ascites fluid instead of the primary antibody in the immunoperoxidase technique. In most cases (10 specimens) T4-positive and T8-positive cells could be classified in about similar numbers, while in two samples more T4-positive cells and in four samples more T8-positive cells were found. But for quantitative analysis of the exact ratio of T4/T8 cells in these circumstances, namely a sporadic distribution in the cornea, a large number of sections from different parts of the cornea is necessary, which we did not obtain.

Discussion

Lymphocytes are present as T cells in the normal human cornea even in absence of any inflammatory process. While they are quite common in the periphery of the cornea, they also occur sporadically in the central part of the cornea. In most corneas T4-positive and T8-positive cells occur in similar numbers. An exact quantitative determination needs large numbers of sections from different parts of the cornea, which were not obtained in this study.

These T lymphocytes probably migrate into the cornea from the limbal vessels. Their exact function in the defence mechanism of the cornea is unknown.

The finding of T4-positive cells in the normal human cornea is of great interest in connection with the possible transfer of the aquired immune deficiency syndrome (AIDS) by a keratoplasty. Since the CD4 (T4) antigen is an essential component of the receptor for the AIDS retrovirus,[7-10] the question arises whether lymphocytes occurring in normal corneas could possibly transmit HTLV-III in corneal grafting, though no transmission of HTLV-III by corneal grafting has yet been reported. HTLV-III has been demonstrated in tears of patients suffering from AIDS.[11] This has led to proposals from the Centers for Disease Control.[12] No advice for corneal grafting was recommended at that time, possibly because no documented case of AIDS transmission by corneal grafting has yet occurred.

The Eye Bank Association of America uses two screening techniques to detect infected donor corneas: (1) identification of high-risk individuals, and (2) seropositivity detected by the enzyme linked immunosorbent assay (ELISA) test.[13] Pepose *et al.*[14] have discussed the safety of these screening methods. Meanwhile HTLV-III has also been demonstrated in corneal epithelial cells of a donor with a positive serum antibody to HTLV-III.[15] The virus was not demonstrated in keratocytes or endothelium of the cornea. Along with these findings corneal grafting bears a so far unknown potential risk of transplanting the infection. We also wish to stress O'Day's point:[13] 'the risk-benefit ratio needs to be considered carefully'.

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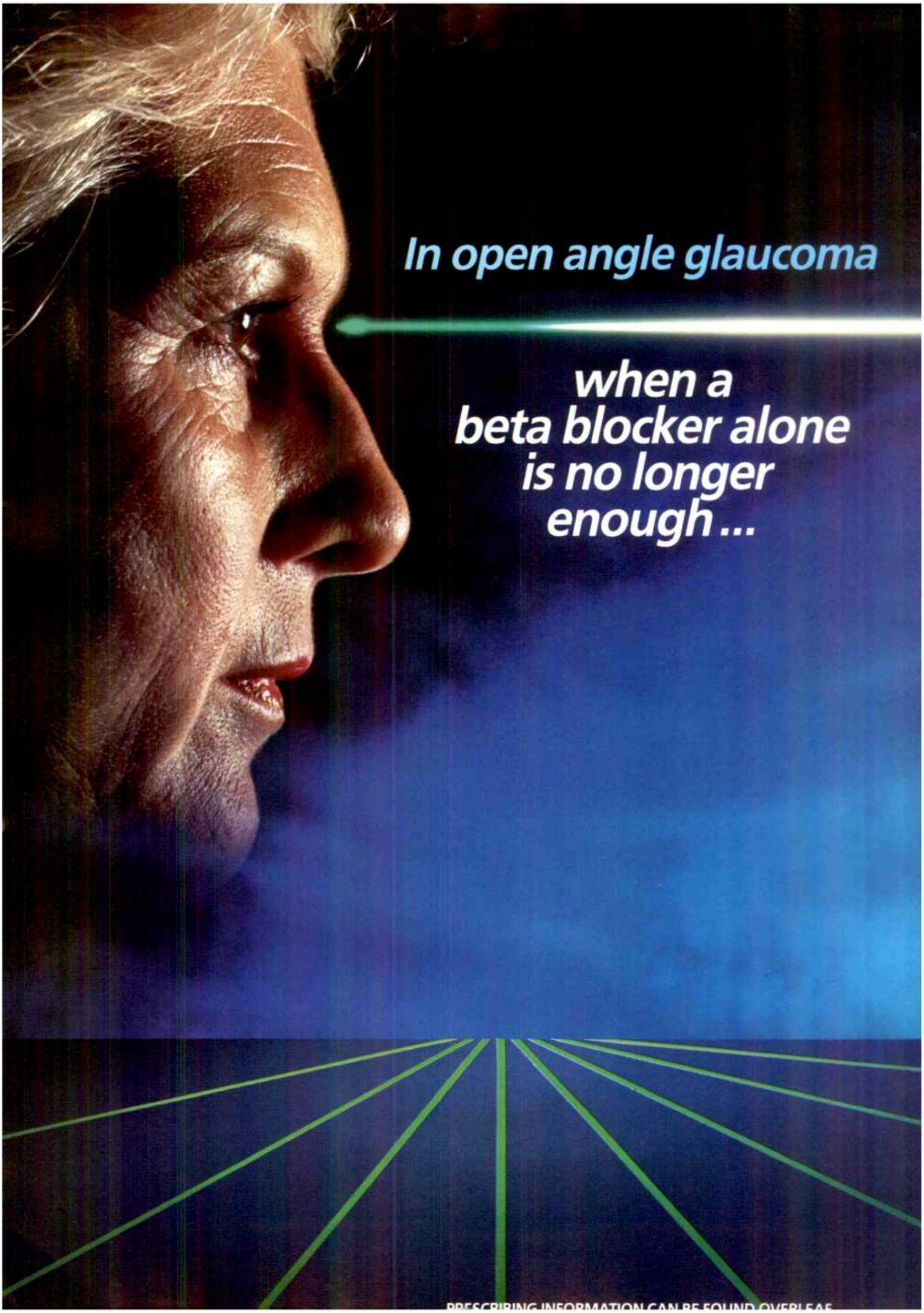
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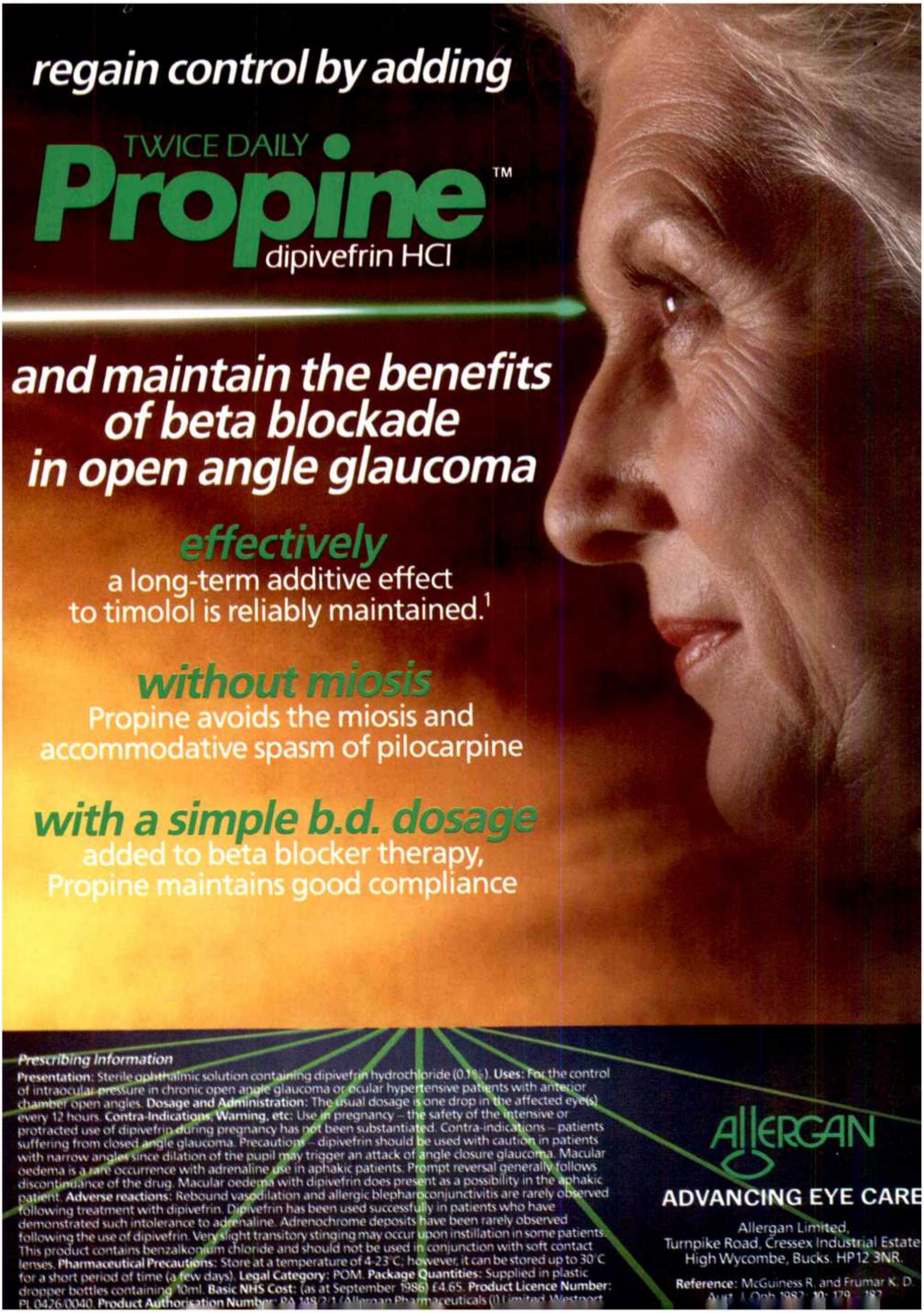

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Short term cyclosporin A treatment of Behçet's disease

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SUMMARY Eleven separate three-month courses of cyclosporin A, an oral solution 10 mg/kg/day, were administered to eight patients with Behçet's disease with sight-threatening posterior uveitis. It was found to be effective in arresting the inflammatory activity in the eye as well as the mucocutaneous lesions of Behçet's disease. Improvement in visual acuity was observed within one week of starting therapy. Severe exacerbations in the ocular and mucocutaneous lesions occurred on withdrawal of the drug. At this dosage side effects included hirsutism in all women, and a slight rise of serum bilirubins in two patients and of blood urea in one patient. The latter two conditions responded rapidly to dose adjustment.

The triple symptom complex comprising recurrent oral and genital ulcerations and relapsing iritis was first described by Behçet in 1937.[1] In addition to the eye lesions conjunctivitis, episcleritis, keratitis, haemorrhage, and cellular infiltration of the vitreous body, originally described retinitis, retinal thrombophlebitis, optic atrophy, and papilloedema have been reported.[2,3] It later became apparent that Behçet's disease is a systemic disorder involving many other organs including joints, blood vessels, the central nervous system, and the gastrointestinal system.[4] The ocular involvement seen in about 47% of cases may lead to complete loss of vision in 15% of them.[5] Studies in rats suggest a pathogenetic role of the retinal S antigen in the development or perpetuation of posterior uveitis.[6] In man triggering this phenomenon in Behçet's disease is unknown.

Cyclosporin A, a potent immunomodulator affecting both the cellular and humoral arms of the immune response,[7] has been found to be effective in the control of inflammatory activity in the eyes of patients with posterior uveitis of non-infectious origin.[8,9] In this investigation 11 separate three-month courses of cyclosporin A oral solution were administered to eight patients with Behçet's disease with sight-threatening uveitis, and its effects on the various manifestations of the disease were assessed. Seven of the patients were followed up for six to 24 months.

Patients and methods

Eight patients with sight-threatening posterior uveitis were included in this study. Behçet's disease was diagnosed in all patients according to the criteria proposed by O'Duffy;[10] requiring three of the following five features to be present either previously or at first attendance: aphthous stomatitis, genital ulcers, dermal vasculitis, uveitis, or arthritis. Either aphthous stomatitis or genital ulcers had to be present for a definite diagnosis. In addition tissue typing and the pathergy test, a non-specific skin hypersensitivity reaction to needle prick, were carried out on each patient. The combined use of HLA B5 and pathergy positivity has previously been reported from this laboratory to be a useful diagnostic marker of Behçet's disease in Turkey.[11] All the eight cases had acute sight-threatening posterior uveitis and retinal vasculitis. Six patients received a three-month course of cyclosporin A. One patient received two and another patient received three separate three-month courses. All patients were required to attend the clinic regularly once a week

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during the first month and biweekly thereafter, and to report new complaints immediately. Follow-up periods ranged from six to 24 months from the beginning of therapy.

Cyclosporin A solution 10 mg/kg/day was given by mouth in one dose in the morning. If it caused serious side effects the dose was reduced to 8-6 mg/kg/day. All other anti-inflammatory and immunosuppressive medications were discontinued as rapidly as possible.

Disease activity in each of the 16 eyes was assessed under four headings: (*a*) anterior chamber, (*b*) vitreous cavity, (*c*) fundi, (*d*) visual acuity. The last was recorded according to the Snellen chart.

Standard methods were used for the enumeration of peripheral blood lymphocytes, E rosette forming cells (T cells), surface Ig-bearing cells (B cells), and the response of blood lymphocytes to phytohaemagglutinin in cultures.[12] In-vivo skin reactivity was assessed by the purified protein derivative (PPD) skin test.

Results

OCULAR DISEASE (Tables 1 and 2)

The anterior chamber was involved in eight and normal in eight eyes before therapy. At the end of three months' therapy with cyclosporin A nine eyes remained unchanged, the inflammatory activity regressed in four eyes and progressed in three eyes.

Vitreous opacities were present in 13 eyes, one was normal, and two could not be examined. At the end of therapy cellular infiltrations had regressed in six, increased in two, and were unchanged in six eyes.

Table 1 *Clinical data*

No.	*Age, sex*	*Oral*	*Genital*	*EN*	*Ocular*	*Arthritis*	*Vascular*
1	33, M	+	+	−	+	+	+
2	22, M	+	−	+	+	−	+
3	24, F	+	+	+	+	−	−
4	32, F	+	+	−	+	+	−
5	29, M	+	−	−	+	+	−
6	34, M	+	+	+	+	−	−
7	23, F	+	+	−	+	−	−
8	33, M	+	+	+	+	+	±

EN=erythema nodosum.

Table 2 *Disease activity before, during, and after cyclosporin A*

	Before	*During*	*After**
Mucocutaneous	8/8	2/8	8/8
Erythema nodosum	3/8	0/8	5/8
Ocular (16 eyes)	16/16	4/16	15/16
Joints: arthralgia	3/8	3/8	3/8
arthritis	0/8	0/8	1/8
Vascular: acute	0/8	0/8	0/8
chronic	3/8	3/8	3/8
Central nervous system	0/8	0/8	0/8

*Two weeks after the withdrawal of cyclosporin A.

Before treatment optic atrophy was present in two eyes, papilloedema in two, macular oedema in four, periphlebitis with haemorrhages and exudates in four, and subhyaloid haemorrhage in one. One eye was normal, and two eyes could not be visualised because of opacified media. At the end of three months' therapy macular oedema had disappeared in three of four eyes and cicatrix formation was observed in the fourth eye. Papilloedema regressed in the two eyes. Vasculitis in the form of periphlebitis, haemorrhages, and exudates regressed in two eyes and remained unchanged in the remaining two. Subhyaloid haemorrhage observed in one eye had regressed by the end of treatment. One normal fundus remained normal. Two fundi were still impossible to visualise.

Visual acuity, reflecting the effects of therapy in all the segments involved, improved in 12 eyes, was unchanged in three, and was worse in one (Table 3).

A rebound phenomenon was observed in all but one case on the withdrawal of cyclosporin A. Cellular infiltrations increased in eight cases previously involved, and anterior uveitis started in four previously uninvolved eyes. Vitreous opacities were observed in all the 13 eyes previously involved and started de novo in one eye. The retinal lesions became more severe in 12 eyes, two eyes were unchanged, and two fundi could not be visualised. One patient (case 5), who did not show any signs of inflammatory reactivation in the eye, had been on long term immunosuppression with cyclophosphamide and steroids before cyclosporin (Table 2).

The follow-up of patients from the end of therapy showed the following findings. The first two patients who had received three and two three-month courses of cyclosporin A treatment respectively ran a stormy course, having frequent attacks of posterior and anterior uveitis. Although they were subsequently put on immunosuppressive therapy with cyclophosphamide, the first developed bilateral optic atrophy and the second unilateral optic atrophy in 24

Table 3 *Summary of the effect of cyclosporin A on activity of ocular disease*

	Number of eyes that could be examined	*Better*	*Unchanged*	*Worse*
Anterior chamber	16	4	9	3
Vitreous	14	6	6	2
Retina	14	8	5	1
Visual acuity	16	12	3	1

months after the beginning of cyclosporin A treatment. The third and fourth patients, both female, became stabilised after the acute exacerbation period on termination of therapy. Although they still had minor attacks of posterior uveitis, they did not develop irreversible changes in the fundi and maintained fair visual acuity in both eyes. The fifth patient had the most stable course among the eight cases; he had been on chronic immunosuppressive therapy with cyclophosphamide and prednisolone before cyclosporin A and was maintained on a lower dose of both drugs after the initial therapy. He experienced no rebound phenomenon on cessation of cyclosporin A, and his vision remained unchanged for 18 months. The sixth patient was lost to follow-up. The seventh and eighth cases were still running fulminant courses 6-9 months after the cessation of cyclosporin A therapy.

EXTRAOCULAR DISEASE

Mucocutaneous involvement comprising aphthous stomatitis, genital ulcers, and folliculitis was improved by cyclosporin A in seven of eight cases. In six cases manifestations of cutaneous disease disappeared completely during treatment. In one patient the frequency, duration, and severity of the oral aphthae diminished during therapy. A rebound phenomenon was observed within one week after the end of therapy in all patients and lasted for several weeks. Erythema-nodosum-like lesions, which were present in three cases before therapy subsided completely during the three months of therapy. Five cases, two of which did not have these lesions before cyclosporin, developed them within two weeks after the end of therapy (Table 2).

Arthralgias reported in three cases before therapy were not influenced by cyclosporin A. One patient who did not have joint complaints before developed arthritis of the left malleolar joint within three weeks after the end of therapy. Four patients with deep vein thrombosis or sequelae of thrombophlebitis did not show any changes during or after therapy.

IMMUNOLOGICAL EFFECTS

Skin reactivity assessed by the PPD skin test was positive in five and negative in three cases before therapy. It remained positive in four of the five cases during therapy. One case was not retested. The mean lymphocyte count in eight cases before therapy was 1·86 (SD 0·67)$\times 10^9$/l and did not differ significantly from the post-treatment value of 1·47 (SD 0·82) $\times 10^9$/l. The mean percentage and absolute number of E rosetting cells (T cells) 42% and 0·78 (SD 0·23) $\times 10^9$/l respectively were similar to the post-therapy counts, 49·5% and 0·73 (SD 0·30)$\times 10^9$/l, respectively. The mean percentage of phytohaemagglutinin responding cells in short term lymphocyte cultures was 54% before treatment and 66% after treatment. The difference was not significant. OKT4/OKT8 ratios determined in two cases did not show appreciable changes from pretreatment values or from normal controls.

SIDE EFFECTS

Measurements of body weight, pulse rate, blood pressure, complete blood counts, determination of serum urea, creatinine, liver function tests, and urine analyses were performed once a week during the first month and once a month thereafter. Paraesthesias, hyperaesthesias, and flatulence/nausea were the most common complaints from the first days of therapy. They were not serious enough to cause modification of the drug dosage. Hyertrichosis developed in each of the three female patients. It started during the second month of therapy and lasted several months after withdrawal, causing serious anxiety but not early cessation of therapy. Mild hyperbilirubinaemia observed in two cases responded promptly to the reduction of the dose of cyclosporin A to 8 mg/kg/day. One patient developed hypertension and urea retention, both of which returned to normal values on dose reduction to 6 mg/kg/day. The same patient developed progressive anaemia not accompanied by other haematological changes. On questioning, one patient complained of a decrease in libido, probably caused by hyperaesthesia in the penis during intercourse (Table 4).

Discussion

Cyclosporin A, in a dose of 10 mg/kg/day, was found to be effective in arresting the inflammatory activity in the eye of patients with Behçet's disease, resulting in a definite improvement in visual acuity. The improvement was rapid. Cellular infiltrates in the vitreous receded within one to two weeks, retinal vasculitis regressed more slowly, and improvement in visual acuity preceded the regression of inflammatory activity by several days in most of the patients. Acute exacerbations of anterior uveitis were also favour-

Table 4 *Frequency of side effects of short term cyclosporin A*

Paraesthesia/hyperaesthesia	6/8	
Flatulence/nausea	7/8	
Hirsutism	3/8	(all females)
Hyperbilirubinaemia	2/8	
Hypertension	1/8	same patient
Urea retention	1/8	
Anaemia	1/8	
Decrease in libido	1/8	

ably affected in a few cases. During the three-month therapy period the mucocutaneous disease showed very little activity, indicating an anti-inflammatory action on the non-ocular manifestations as well.

All the patients except one experienced acute exacerbations in the ocular and mucocutaneous diseases within one week after the withdrawal of cyclosporin A at the end of three months. It was noted that, although cyclosporin seemed to be less effective in controlling the inflammatory activity in the anterior chamber, on its withdrawal a flare-up of inflammatory activity occurred in the anterior chamber as well as the posterior segment of the eye. The acute increase in the inflammatory activity in all the segments resulted in a significant decrease in visual acuity. The rebound phenomena observed in the mucocutaneous disease accompanying acute exacerbations in the ocular manifestations suggest the possibility of a generalised increase in the inflammatory activity in all the organs usually involved in Behçet's disease.

In order to ascertain the long term effects of cyclosporin A on the outcome of ocular involvement in Behçet's disease, all the cases but one are being followed up closely. The first two patients who have been followed up the longest have continued to have frequent ocular attacks resulting in serious damage. In the last two patients the disease seemed to behave similarly during the first six to nine months off therapy. Three patients who did not have as severe rebound phenomena as the others seem to run more stable courses off therapy. Since all these patients had been selected for cyclosporin A therapy because of their fulminant, sight-threatening ocular disease, this result does not seem as discouraging as it appears.

The mode of action of cyclosporin A on the various inflammatory phenomena in Behçet's disease is unknown. Various immunological disturbances have been reported in Behçet's disease,[13 14] but there is no direct evidence that the inflammatory lesions in various organs are immunologically mediated. Cyclosporin A is thought to influence the early phase of the immune response by blocking the synthesis and/or release of IL-1 from macrophages and IL-2 from helper T cells.[15 16] If this blockade is the cause of the anti-inflammatory action of cyclosporin A, it is rapid and transitory. To gain any lasting benefit a long term treatment plan with cyclosporin A with or without other immunosuppressive or anti-inflammatory drugs should be considered.

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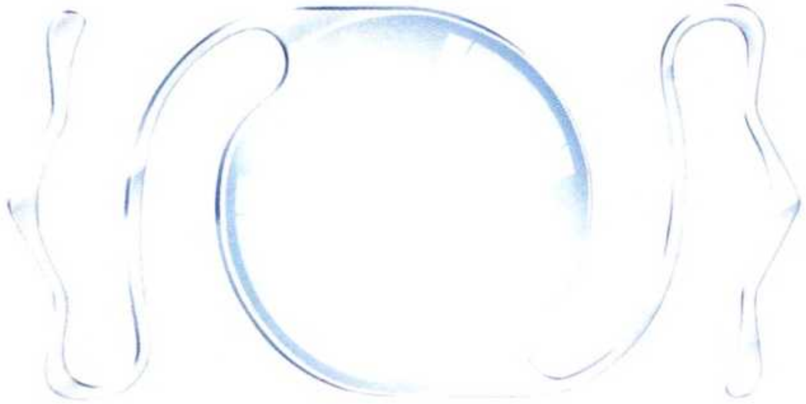

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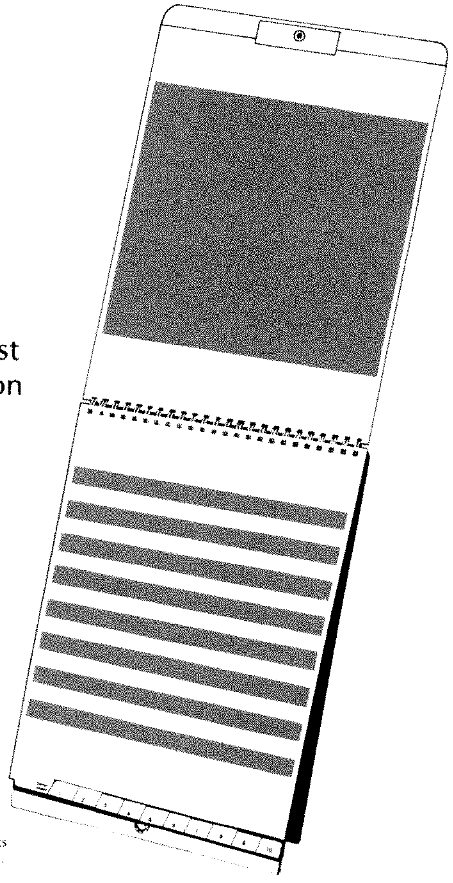

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Intraocular pentastomiasis causing unilateral glaucoma

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SUMMARY We present a case of intraocular pentastomiasis in a 12-year-old Israel Arab boy. A single secondary pentastomid larva, most likely of *Linguatula serrata*, was found in the anterior chamber of the right eye, attached loosely to the pupil's border by a fibrinous mass. Associated conditions were iritis, subluxation of the lens, and secondary glaucoma. This is the first documentation of human pentastomiasis in Israel.

Cases of human pentastomiasis involving the eye are relatively rare. In so far as we have been able to trace them, there are only 10 previous reports of ocular pentastomiasis: four of these are from the USA and were due to larval *Linguatula serrata*[1-4]; the remaining six are from Africa and were caused by *Armillifer armillatus*.[5-10]

The present case is of an Israeli Arab boy who suffered from unilateral glaucoma secondary to iritis which was provoked by a larval Lingutulid. This is the first report of human pentastomiasis from Israel.

Case report

A 12-year-old Israeli Arab boy from a neighbouring village was referred to our clinic because of high intraocular pressure in his right eye. The boy said he had suffered pain in his right eye for about a week, beginning after 'something believed to be a fly hit it'. On admission he had a visual acuity of 30 cm finger counting on the affected right eye. The intraocular pressure was 48 mmHg by applanation. The cornea was oedematous, with some flare in the anterior chamber. The pupil was 3 mm wide, round and free, the lens clear but with partial iridodonesis on the lower nasal quadrant. On ophthalmoscopy there was a glaucomatous cupping of 0·8 cup/disc ratio in the optic disc. Gonioscopy revealed several anterior goniosynechiae, particularly at 9 and 11 o'clock. The visual acuity of the left eye was 6/6, the intraocular pressure was 12 mmHg, and the anterior and posterior segments were normal.

Secondary glaucoma of the right eye was diagnosed and the boy was given tablets of acetazolamide 0·125 g four times a day, topical drops of homatropine 1% with topical steroids three times a day and timolol maleate 0·25% twice daily. The following day, on mydriasis, a subluxation of the lens was observed. The intraocular pressure diminished to 28 mmHg but increased again to 35–40 mmHg on subsequent days. Nine days after admission, and on failure of the conservative treatment, an uneventful trabeculectomy was performed.

On the first postoperative day, in the course of slit-lamp examination, we noticed a white segmented mass in the anterior chamber which was encased in a fibrinous sheath and attached loosely to the pupil's border at 12 o'clock (Fig. 1). This fibrin coated and slightly crescent shaped mass changed its position several times during the next few days. Laboratory tests, including a complete haematological examination, gave normal results. Stool examinations for parasites were negative. Meanwhile there was no alleviation of the intraocular pressure.

One week after the trabeculectomy the mass was removed from the anterior chamber via limbal paracentesis. We were obliged to cut the fibrinous sheath in order to liberate the segmented mass and to take it out. After this procedure the eye became less irritated, and in the next few days the intraocular pressure decreased markedly, to stabilise at 13–14 mmHg.

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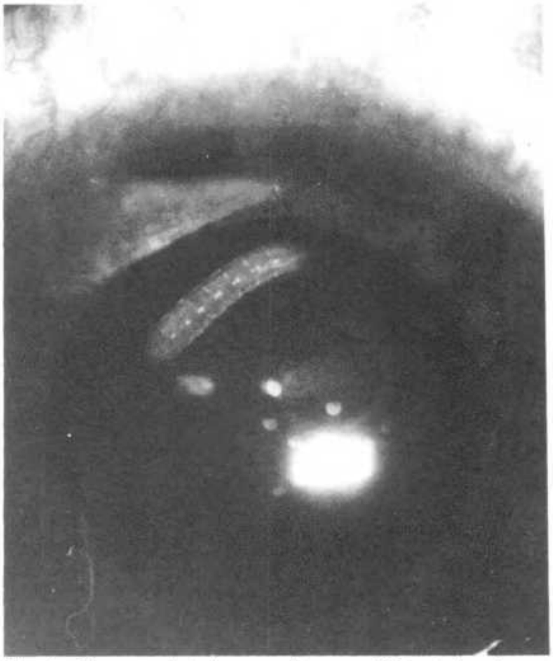

Fig. 1 *Photograph (taken at a distance of 35 cm) showing slightly crescent shaped foreign body loosely attached to the right eye pupil at 12 o'clock. This was diagnosed as a second stage pentastomid larva, most likely of* Linguatula serrata.

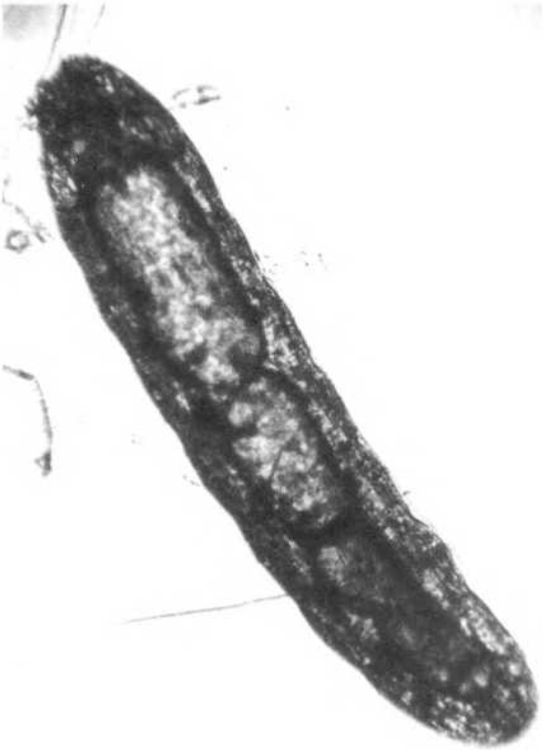

Fig. 2 *The pentastomid larva after removal from its fibrous encasement. The specimen had undergone partial decomposition, but body cavity and openings at both ends were still discernible. The body of larva is only very sparsely annulated.* × 9.

Three weeks later the patient was discharged home. The visual acuity of the affected eye was then 1/2 a meter finger counting and the intraocular pressure was 10 mmHg. The anterior segment was normal apart from the existence of fibrin remnants in the anterior chamber, which were stretched over the lens and were attached to the limbal wound. On ophthalmoscopy the optic disc appeared pallid. The fellow eye seemed to be the same as on admission.

After he was discharged the boy was lost to follow-up for almost a year. When he was traced and examined at our outpatient clinic, there was no change in the intraocular pressure of the right eye, and the visual acuity was about the same as on discharge. However, a cataract had begun to develop, and the optic disc seemed to have undergone atrophy.

PARASITOLOGICAL FINDINGS

The extracted fibrinous mass had to be cut through in order to release the object contained inside. Once freed, the latter could be examined under the dissecting microscope and later cleared in 10% KOH. The object measured 2·3 mm in length and 0·5 mm in maximal width. It appeared to have undergone some decomposition within its fibrinous sheath, and at first glance its cylindrical and slightly annulated shape was reminiscent of a fly larva (Fig. 2). However, closer examination after clearing failed to reveal the characteristic mouth hooks and posterior spiracles of the fly maggot, but instead showed the incipience of the anterior fang-like hooks typical of pentastomid infective stages (Fig. 3). Under higher magnification the fine spination of the cuticle was revealed (Fig. 4), and this, together with the size measurements, the absence of massive annulation of the body, and the geographic location, finally led us to identify the object as a secondary (second-stage) linguatulid larva (nymph), most likely of *Linguatula serrata*.

Discussion

The pentastomes or pentastomids are haematophagous metazoan endoparasites that as adults live in the lungs of reptiles and birds or in the nasopharynx of mammals, usually carnivores. The larval-nymphal

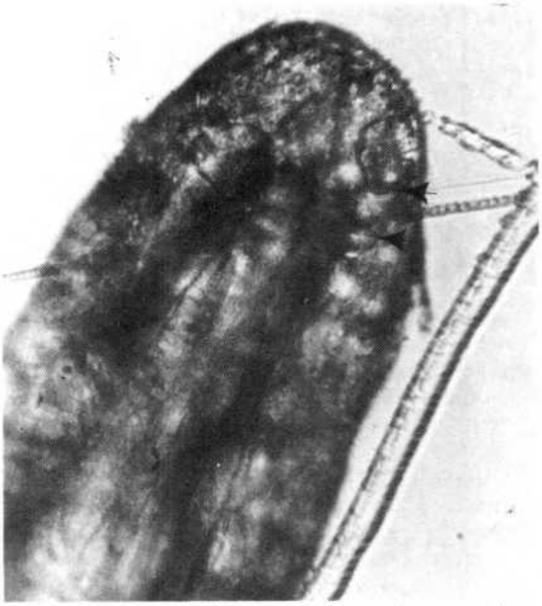

Fig. 3 *Anterior end of pentastomid larva. Arrows mark incipient hooks on the one side. Spination of cuticle discernible at anterior margin on right.* × *18.*

stages develop in a wide variety of vertebrate intermediate hosts, including man. Man, however, is usually an aberrant intermediate host, representing a dead end for the parasite.[11] The taxonomic position of pentastomes is still obscure, and exact details of the life cycles of most of the species are little known. The pentastomes seem to occupy an intermediate position between annelids and arthropods and have been assigned to a separate phylum (Pentastomida[11,12]), but a more recent view[13] is that they are a subclass within the Crustacea. Only six species of pentastomes are known to infect man, and of these, two species, namely, *Armillifer armillatus* and *Linguatula serrata*, account for more than 99% of reported cases of human pentastomiasis.[11] The former is a species limited to Africa, while the latter has been recorded from man in Africa, Europe (Germany, Switzerland, Italy, Greece, and Turkey), the Near East and Middle East, and the American continent (Brazil, Chile, Colombia, Panama, Mexico, Cuba, and the USA).[11,13]

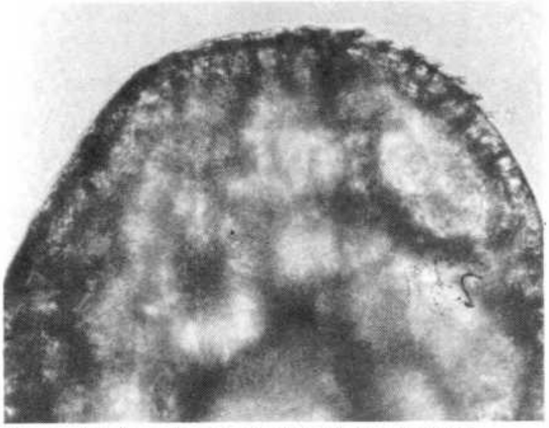

Fig. 4 *Further enlargement of anterior extremity of pentastomid larva revealing the spination (visible on right side) exclusive to pentastomids of genus* Linguatula. × *24.*

The present intraocular case was diagnosed as due to a species of *Linguatula* and this for several reasons. Firstly, our patient has never travelled abroad. This rules out *Armillifer armillatus* and the related *A. grandis*, which are strictly African species. Secondly, the definitive hosts for *Armillifer* species are snakes of the genera *Python* and *Bitis*,[14] and neither of these is represented in Israel. Thirdly, by its length (2·3 mm) the pentastomid removed by us occupies an intermediary position between the length ascribed by Hobmaier and Hobmaier[15] for the second stage (0·35–0·5 mm) and third stage (4–6 mm) larva of *Linguatula rhinaria*, now regarded as a synonym of *Linguatula serrata*.[16] Finally, and most importantly, of third stage pentastome larvae (nymphs) encountered in man all have a smooth cuticle except those of species of *Linguatula*, whose conspicuous spinules are sufficient to differentiate them from all the rest.[11] As Fig. 4 shows, our specimen bears the rudiments of such spination, although it still lacks the massive body annulation and the crescent or cashew nut shape of the infective, third stage larva.[11]

As mentioned earlier, our patient has never travelled abroad, so clearly the infection was contracted locally. Ours is the first report of human pentastomiasis in Israel, and in view of the geographic location it is almost certain that we are dealing with a larval stage of the species *Linguatula serrata*. The adult stages of this species reside in the nasopharynx of carnivores, mainly dogs and cats, and these abound in Israel as well as in neighbouring Lebanon, where 44·3% of street dogs in Beirut have been found to harbour *L. serrata*.[14]

The life cycles of most species of pentastomes have not been adequately studied, but that of *L. serrata* is fairly well known thanks, inter alia, to Hobmaier and Hobmaier.[15] Briefly, the developmental cycle requires carnivores (dogs and cats) as definitive hosts and herbivorous animals, mainly sheep and goats, as intermediate hosts. However, various other mammals, including man, can also serve as intermediate host. Eggs of the parasite, which are laid in the upper air passages of the definitive host, are passed to the exterior in its sputum or faeces, whence they are ingested by the intermediate host with contaminated forage or water. The eggs hatch in the intestine, and the liberated first stage larvae, rarely exceeding 250 μm in length, penetrate the intestinal wall and migrate in the abdominal cavity to settle and ultimately encyst in various organs but mainly in the liver and lymph nodes. After several moults within the cyst, the third stage larva (also called nymph or juvenile) emerges from its cyst to migrate again through the peritoneal cavity before re-encysting in various tissues and organs. When these are now consumed by the carnivorous definitive host, the infective larva excysts to travel via the stomach and oesophagus to the nasopharynx, where, after several additional moults, it attains sexual maturity.[11 13 14]

Man—an aberrant intermediate host—usually acquires the infection from egg contaminated vegetables or water, or perhaps from intimate contact with an infected cat or dog,[11] but also can become infected by consuming the raw liver and/or lymph nodes of sheep and goats which contain the encysted tertiary linguatulid larvae. The latter form of human pentastomiasis, characterised by severe nasopharyngitis, is called the halzoun or marrara syndrome,[17] and is prevalent in Lebanon, Turkey, and Greece.[11]

The present and similar cases of ocular pentastomiasis pose the interesting question as to how the parasite reaches this organ. The question has intrigued several investigators[1 18] and has yet to be resolved. In the present instance the patient claimed to have been hit in the eye by a fly a week prior to his admission. Some flies, such as *Oestrus ovis*, do infest the human eye with their maggots, producing ophthalmomyiasis, but there is no record as yet of flies serving as vectors of pentastomes, though there has been one report of a cockroach (*Periplanata americana*) serving as intermediate host for a lizard pentastome.[19] Moreover, the finding of a unilateral glaucomatous excavation of the optic disc and the presence of several goniosynechiae in the boy's right eye strongly suggest a parasitic infection of a much longer duration than one week.

From the life cycle of pentastomes, as briefly described above, it is clear that both the first stage larva (emerging from the egg) and the third stage larva (after excystment) have a propensity for migration in the body of the host. Might not the microscopic first stage larva, which rarely exceeds 250 μm in length, inadvertently enter a blood vessel, in the course of its penetration through the intestinal wall, and be transported to the eye? We believe this is at least theoretically feasible, and other parasites, such as *Entamoeba histolytica*, do occasionally travel in the blood stream to reach the human brain. Since the migratory pentastome stages are endowed with proteolytic capabilities, these could explain the observed zonulolysis and subluxation of the lens in the present case. Alternatively, in the cases of halzoun syndrome, might not the liberated third stage larva accidentally travel from the nasopharynx to the eye via the nasolacrimal duct, which is a sufficiently wide, non-ciliated passageway? We believe this to be an equally feasible explanation for some cases of ocular involvement due to *Linguatula serrata*, but in our case the first conjecture is preferable because the recovered parasite was apparently a second stage larva and there was no history of halzoun. The infection could readily have been acquired from egg contaminated vegetation or water, because the boy lived under very poor sanitary conditions and admitted drinking water from doubtful sources.

Localisation of pentastomid larvae in the anterior chamber is apparently rare, for only a few cases have been reported.[1–3 9] Ocular manifestations of pentastomiasis are equally rare, and indeed Fain[16] refers to ocular infections as being free of lesions. Our case, however, did involve unilateral glaucoma secondary to iritis and in this respect and also in its aetiology, is almost identical to that reported by Deweese *et al.*[3] from a Negro girl.

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Ocular larva migrans: a case report

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SUMMARY A case of intraocular toxocara larva migrans occurring in a 12-year-old boy is presented. Motility is inferred from the nature of multiple intraocular lesions observed. Possible mechanisms preventing a conclusive immunological response to the organism are discussed.

Ocular toxocariasis continues to present the ophthalmologist with a problem of diagnosis despite improved investigative tools. Several clinical patterns of presentation are recognised.[1] One of these, the motile chorioretinal nematode, has been described following ophthalmoscopic visualisation,[2,3] and inferred from the discovery of a subretinal tube on histological examination of a presumed case of ocular toxocariasis.[4] We present a case of ocular toxocariasis in a 12-year-old boy which purports to demonstrate the intraocular motility of the toxocara larva and the nature of the various lesions caused by its passage. We relate the difficulty in achieving serological confirmation of ocular toxocariasis to peculiarities in the intraocular host-parasite relationship.

Case report

A 12-year-old boy first attended the ophthalmic outpatient clinic of the Royal Victoria Hospital, Belfast, on 26 March 1985. He complained of a disturbance of vision in his left eye, present for approximately six weeks.

Three weeks after the onset of symptoms the patient found he was unable to see out of the left eye, and since then there had been no recovery of vision. The affected eye was comfortable. There was no history of injury, ocular inflammation, or discharge. The patient was in good health otherwise, though he suffered from intermittent attacks of asthma which were treated with a salbutamol inhaler. The asthmatic attacks were precipitated occasionally by contact with a pet rabbit. There was no obvious contact with dogs, cats, or farm animals. At the age of 6 years the patient was admitted to hospital suffering from febrile convulsions. No specific diagnosis was made and convulsions have not recurred. There was no family history of any ocular or relevant systemic disease.

EXAMINATION

At the first examination, on 26 March 1985, the visual acuity of the unaided right eye was recorded as 6/4 and that of the left eye as accurate projection of light. Examination of the right eye showed it to be structurally sound in all regards. The left eye was injected, and biomicroscopy revealed slight flare and some inflammatory cells in the anterior chamber. Pigment deposits on the anterior lens surface and posterior synechiae were present (Fig. 1). The intraocular pressure was 18 mmHg on the right and 24 mmHg on the left. The left lens was clear, but immediately behind the lens there was a grey-white intraocular membrane or mass associated with an array of dilated vascular channels and pigment deposits. The ocular fundus could not be visualised.

Systemic examination was negative, with no evidence of regional or generalised lymphadenopathy, skin lesions, arthropathy or hepatosplenomegaly.

The right visual field was normal (Goldmann perimetry) but it was not possible to obtain a plot on the left side. Electroretinography showed a normal B wave amplitude on the right side, but recordings on the left side were extinguished, even to a bright flash. Fluorescein angiography (Fig. 2) confirmed the presence of numerous dilated shunt-like blood vessels within the retrolenticular mass. These blood vessels filled rapidly in the early phases of angiography; the major channels remained competent, while the smaller vessels leaked dye, causing the retrolenticular mass to become hyperfluorescent by the later angiographic frames. Some of the large

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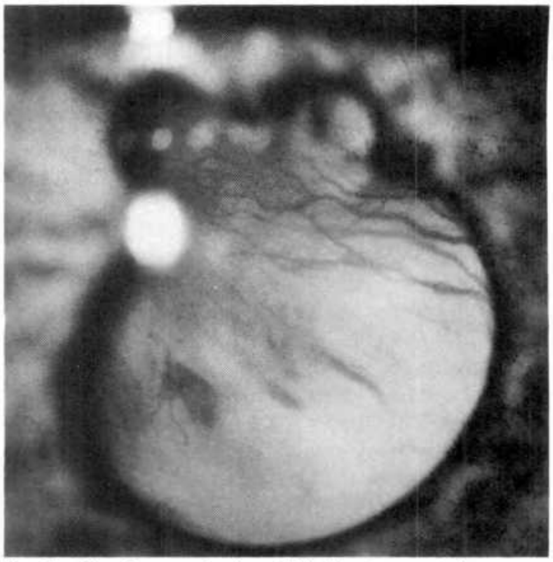

Fig. 1 *Biomicroscopic view of iris showing posterior synechiae and the vascular cyclitic membrane.*

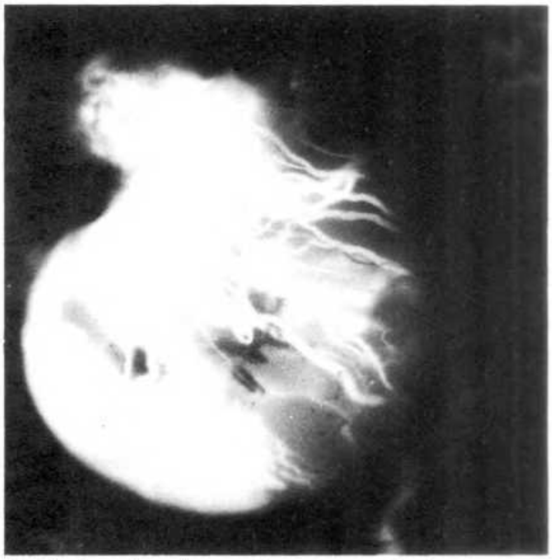

Fig. 2 *Late phase fluorescein angiogram showing large vascular channels within retrolental membrane.*

vessels remained non-perfused throughout the angiographic series, which was consistent with either thrombosis or the 'steal phenomenon' seen in tumour circulations. The late phase angiograms showed leakage of dye at the superior iris, but there was no evidence of rubeosis iridis.

The white blood cell count was $6{\cdot}5\times10^{9}$/l and the eosinophil polymorphonuclear count was $0{\cdot}26\times10^{9}$/l or 4% of the differential white cell count. The erythrocyte sedimentation rate (ESR) was 33 mm in the first hour. The blood alkaline phosphatase at 182 ml/l; (considered raised in an adult but within normal range for a child of 12 years of age) was the only biochemical finding. The Rose-Waaler test and serological tests for Rh factor and rheumatoid arthritis factor (latex) were negative. Serological tests for toxoplasmosis were negative. The toxocara antibody enzyme linked immunosorbent assay (ELISA) test was weakly positive (0·63 units: normal values 0–0·50). Chromosome analysis showed no abnormalities.

X-ray examination of the chest showed nothing unusual except for an abnormality of the pulmonary conus, which was not considered significant. *X*-rays of the left orbit were normal, and there was no evidence of intraocular calcification. Ultrasound examination identified a retrolenticular mass consisting of a dense posterior cyclitic membrane and a funnel shaped retinal detachment. CT scanning showed a distinct abnormality of the left eye, the globe appearing to be of increased attenuation, with an area of further increased attenuation noted posterolaterally. The appearance of the CT scan suggested to the radiologist 'a malignant tumour within the globe which may have arisen from the retina'.

MANAGEMENT

The patient was followed up for four weeks, during which time the visual acuity diminished to no perception of light in the left eye and the intraocular pressure fell to 4 mmHg. In view of the loss of visual function, impending ocular hypotony, and the suggestion of the presence of an intraocular tumour on CT scanning, enucleation of the left eye was carried out on 30 April 1985.

PATHOLOGICAL FINDINGS

The globe was fixed in formalin prior to processing and embedding in wax. Macroscopically the left eye measured 23×23×22 mm and showed no gross external abnormality. The cut surface showed an apparently normal anterior chamber. A cyclitic membrane posterior to a normal lens with an adherent funnel shaped detachment of the retina was present.

Histological examination of serial sections showed a normal cornea, filtration angles, iris, and lens. A cyclitic membrane (Fig. 3) extended from one part of the ciliary body, posterior to the lens, to the contralateral aspect of the ciliary body. This membrane consisted of three generations of inflammatory tissue. These showed resolved and resolving inflammation with fibrinous organisation and more recent

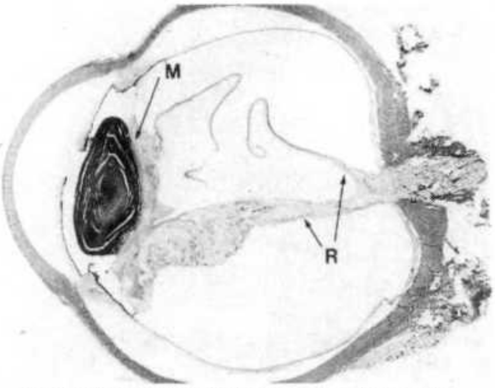

Fig. 3 *Histological section of whole eye showing cyclitic membrane* (M) *and funnel shaped detachment of the retina* (R).

inflammation composed of loose, oedematous, serofibrinous material infiltrated mainly by eosinophil polymorphonuclear leucocytes but including some neutrophil polymorphs, lymphocytes, and plasma cells. Large blood vessels were readily apparent. The membrane extended over the inner aspect of the retina producing a tractional retinal detachment.

The retina was well preserved in most areas, which confirmed that the detachment was a recent occurrence. There were two foci (Fig. 4) of eosinophilic necrosis with the features of the Splendore-Hoeppli phenomenon[5] situated in the outer retina. No organism or remnants of an organism were found in either of these lesions. One lesion contained Charcot-Leyden crystals. Elsewhere in the posterior retina there was perivascular chronic inflammatory cell infiltration.

The choroid contained foci (Fig. 5) of eosinophilic polymorphonuclear inflammation. One of these focal lesions showed a perforated Bruch's membrane partially damming back the eosinophils and necrotic eosinophilic material to cause a dark staining area on the choroidal aspect. Eosinophilic material exuded through Bruch's membrane, detaching the retinal pigment epithelium. No organism or remnants of an organism was found in this lesion. The remainder of the choroid showed low grade chronic inflammation and a relative absence of eosinophils.

In the subretinal space four separate discrete spheroidal coagula (Fig. 6) were found. These consisted of relatively acellular hyaline material containing pigment debris from the retinal pigment epithelium. A few macrophages were seen on the surfaces of these coagula. No organism or remnants of an organism was found in any of these four lesions.

On level 152 of the serial histological sections a granuloma (Figs. 7 and 8) composed mainly of lymphocytes, plasma cells, macrophages, foreign body type giant cells, and a few eosinophils was seen in the subretinal space. This lesion contained a larva of *Toxocara canis* with characteristic morphological and structural features.[6]

Discussion

We have demonstrated eight lesions in this eye associated with ocular toxocariasis, raising the question of how many larvae were involved in their production. It is our contention that only one larva rather than up to eight was involved, as only one larva was found after serial sectioning of each of the other seven lesions. There was evidence of sequential

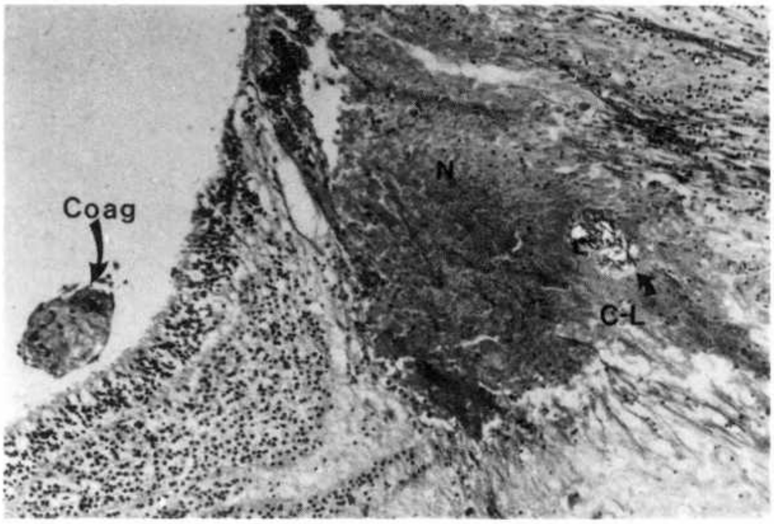

Fig. 4 *Histological section of the outer retina showing an area of eosinophilic necrosis* (N) *with foci of Charcot-Leyden crystals* (C-L, arrowed). *Also present is a subretinal coagulum* (Coag). *H and E, polarised light.* × *52.*

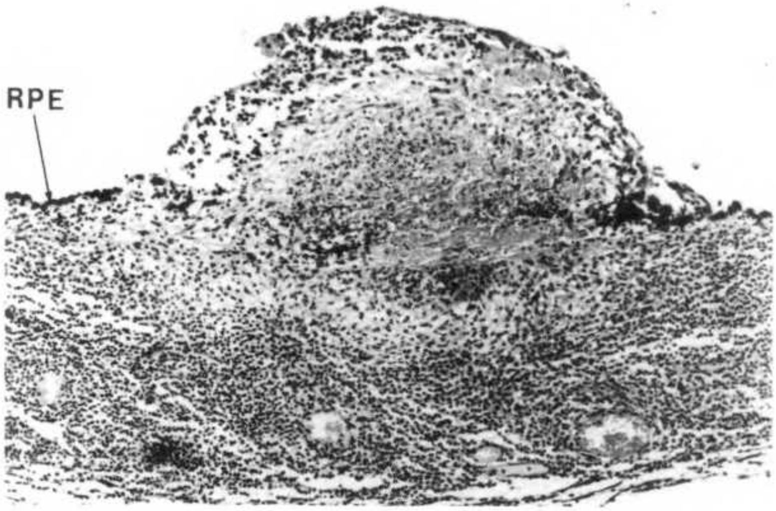

Fig. 5 *Histological section of choroid showing an eruption composed mainly of eosinophils and detaching the overlying retinal pigment epithelium* (RPE). *H and E. × 52.*

(rather than synchronous) inflammatory events giving rise to several 'waves' of cyclitic membrane formation and chorioretinal lesions at different stages of development or degeneration. Furthermore, there was no indication of worm infestation of the fellow eye or systemically.

The lesions we have described seem to represent different stages of the immunological reaction by the host to the parasite. The immediate reaction, surrounding the larva, consists mainly of lymphocytes, macrophages, and a few eosinophils.[7] In the subjacent choroid, eosinophilic polymorphonuclear leucocytes have accumulated and intensified the focal inflammatory response, eventually erupting through Bruch's membrane to attack the larva within the subretinal space. This choroidal lesion is characterised by an area of eosinophilic necrosis, surrounded by viable eosinophils, which extrudes through a perforated Bruch's membrane to elevate the overlying retinal pigment epithelium. The choroidal eruption appears to have resolved, giving rise to an expended coagulum as seen in the subretinal space and possibly the Splendore-Hoeppli phenomena.

It is possible to plot the path (Fig. 9) taken by the larva in the vitreous and subretinal space, deducing the chronological order from the type and age of the eight lesions present in this case. The likely sequence of events is that the larva entered the anterior vitreous from a peripheral branch of the retinal artery, initiating the reaction that caused the cyclitic membrane. The topography of the blood vessels identified in the cyclitic membrane suggests that the

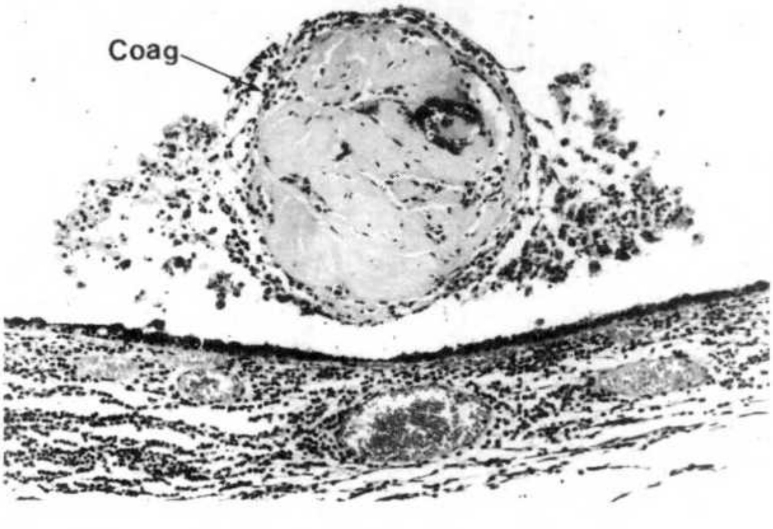

Fig. 6 *Histological section of a subretinal coagulum* (Coag) *surrounded by macrophages and remnants of a choroidal eruption. H and E. × 52.*

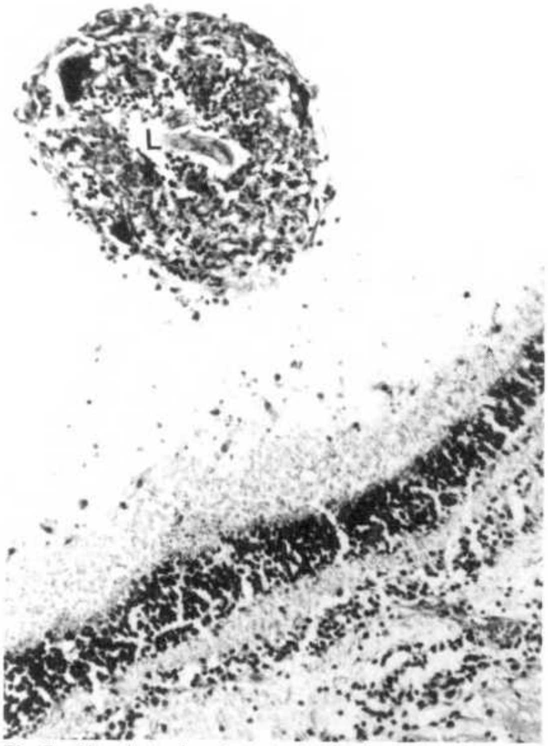

Fig. 7 *Histological section of subretinal granuloma* (L), *which includes a toxocara larva. H and E. × 57.*

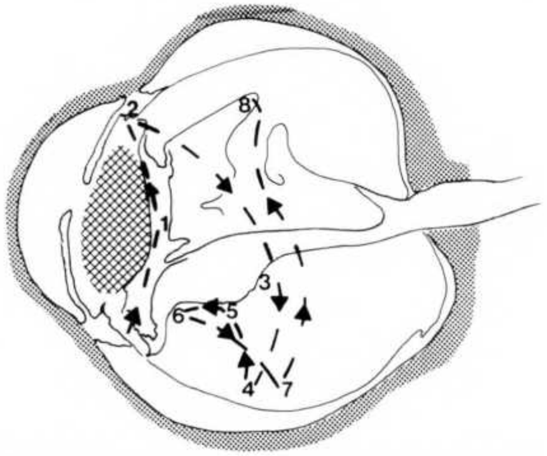

Fig. 9 *Drawing of the eye depicting the presumed path of the toxocara larva. (1) Entrance to vitreous from retinal circulation. (2) Site of coagulum at point of entry to subretinal space. (3, 4, 5) Sites of subretinal coagula. (6) Sites of Splendore-Hoeppli phenomenon. (7) Site of choroidal eruption. (8) Site of subretinal granuloma containing the toxocara larva.*

larva moved from one part of the ciliary body to a contralateral site and then gained access to the subretinal space. Within the subretinal space the larva moved freely. Such motility of the toxocara larva and presumed helminths within the eye has been reported in experimental toxocariasis in the eyes of mice[8,9] and primates,[10] by the presence of a subretinal tube in one case report,[4] and by clinicians on ophthalmoscopic examination.[2,3]

This case is an example of the clinical dilemma of differentiating between a malignant intraocular tumour and other benign intraocular lesions despite possession of an array of sophisticated and sensitive

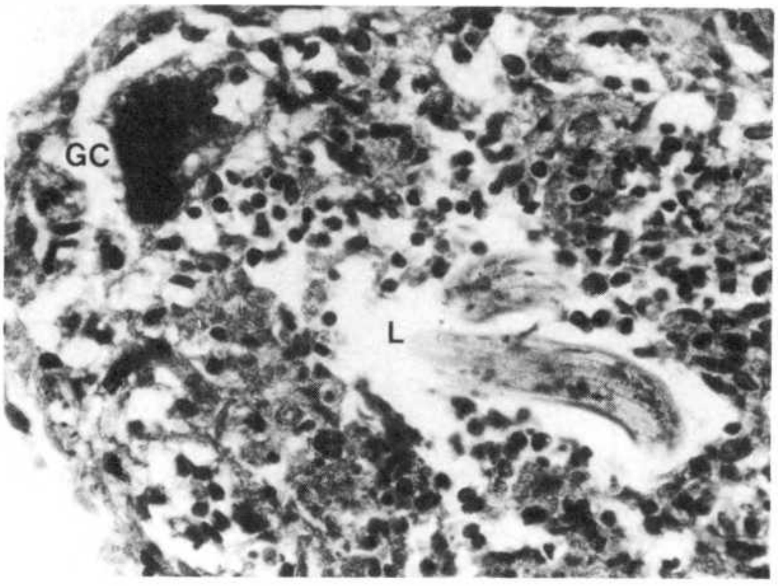

Fig. 8 *Histological section of subretinal granuloma showing a toxocara larva* (L) *and a giant cell* (GC). *Note the paucity of eosinophils. H and E. × 52.*

diagnostic tests. Of particular interest is the relatively low eosinophil polymorph count ($0\cdot26\times10^{9}$/l or 4% of WBC) in the peripheral blood (normal values in children $0\cdot03$–$0\cdot7\times10^{9}$/l)[11] and the barely positive ELISA titre for toxocara, when compared with the pronounced inflammatory reaction in the eye as seen on histological examination. There is no evidence that this host (in common with the patients in previous reports)[12] was immunologically compromised or deficient before or after clinical presentation.

Previous reports[13] support the contention in this case that the worm load in patients with ocular toxocariasis is low. This may result in an appropriately slight immunological response by the host.[14] The findings in our case strongly suggest that the larva of toxocara can move away from an inflammatory response to its presence. It is probable that in this process the parasite manipulates its antigenic profile by shedding its 'coat' (glycocalyx)[15] Thus residual antigenic material continues to stimulate the inflammatory response while the parasite in a new guise moves elsewhere. A change of antigenic profile serves to prevent a concerted antibody response by the host, as each change of surface antigens requires synthesis of a new set of antibodies to combat them.[16]

A further factor in the host-parasite relationship peculiar to the eye may be the immunological surveillance of the subretinal space. The outer retina and the subretinal region are nourished and serviced by the choroidal circulation. It would appear that the initial response via the retinal circulation and the subsequent choroidal reaction may be delayed or curtailed by the inner and outer blood retinal barriers respectively. The evidence from our case suggests that the response to the larva in the subretinal space is a granuloma closely followed by a choroidal eruption consisting predominantly of eosinophils, bursting through Bruch's membrane into the subretinal space in a bid to attack the parasite before it moves on. This obviously works in some instances, as previous case reports have described the remnants of larvae in similar isolated chorioretinal lesions.

This case appears to represent an intermediate stage between a solitary choroidoretinal lesion[12] and nematode endophthalmitis[17] in the destruction of an eye by the toxocara larva. The histopathological appearances show that the larva can defend itself by moving within the subretinal space. It is also suggested that the response of the host is attenuated by an inadequate immunological surveillance of the subretinal space with inner and outer blood retinal barriers obstructing a concerted immunological response to the organism. It is perhaps for these reasons and the scant number of parasites that the eosinophil count and ELISA titre are so low despite the presence and activity of the larva. Such a hypothesis suggests that an organism in the eye could easily give rise to a negative or dubious positive result on examination of the peripheral blood. This situation will lead to a continuation of the diagnosis of 'choroidoretinitis' due to presumptive toxocariasis in clinical ophthalmic practice, despite the availability and use of sensitive serological tests.

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Book reviews

An Atlas of Diseases of the Eye. 3rd Edn. By ES Perkins, Peter Hansell, Ronald J Marsh. Pp. 90. £14·95. Churchill Livingstone: Edinburgh. 1986.

The third edition of this excellent atlas fully lives up to its predecessors and has a completely revised layout. With the inclusion of fluoroscein angiograms, line drawings, EMI scans, and the like the value of the colour illustrations is considerably enhanced. The purpose of the book is to provide medical students, general medical practitioners, specialists in branches of medicine other than ophthalmology, and ophthalmologists in training with an illustrated guide to the more common and important ocular disorders.

The book is 90 pages long with half of the pages devoted to illustrations, mainly in colour. The quality of the illustrations is high and the colour reproduction excellent. The book admirably fulfils its stated purpose. The text is brief but appropriate and the authors are to be congratulated on producing a very comprehensive illustrated guide to clinical ophthalmology in a very small compass. W S FOULDS

Pathology of the Eye. By GOH Naumann and DJ Apple. Pp. 998. DM720·00. Springer-Verlag, Berlin: 1986.

In 1980 Professor Naumann, assisted by a small number of coauthors, wrote a comprehensive textbook of ocular pathology which was distinguished by its accuracy, clarity, good illustrations, numerous tables, and informative line diagrams. Combined with a high standard of production this made for a first-class contribution to the field, and the few complaints of substance concerned its inaccessibility to those who could not read German and its cost.

The first but not the second cause for complaint has now been removed in this translation by one of the original contributors, Dr Apple. Opportunity has been taken to bring the text up to date and to add many more references.

A brief description of ocular anatomy, development, and investigative histopathological techniques is followed by a moderately detailed account of the normal microscopical appearances of the eye. Chapters dealing with developmental anomalies, intraocular inflammation (the latter perhaps a little confused in its organisation and aims), and trauma are next. Then come 10 chapters dealing with the pathology of individual ocular tissues and structures. Sections on ocular manifestations of systemic disease and toxic reactions complete the contents.

Recent years have seen the publication of several excellent contributions to the literature of ophthalmic pathology, so how does the present text compare? Written with clinical ophthalmologists in mind, it is factual, with emphasis on morphological findings, and it avoids the excesses of speculation which detailed discussion of pathogenetic mechanisms can invite. The information given is sound and precise, and the supportive photographs are well chosen even if, inevitably, other than in an extended atlas, many conditions are not illustrated. The acid test is whether it can be recommended to one's students, and for my part the answer is unequivocally in the affirmative provided they can beg, borrow, or steal a copy, because few will be able to afford to buy it. ALEC GARNER

Ocular Pathology. 3rd Edn. Clinical Applications and Self-Assessment. By David J Apple and Maurice F. Rabb. Pp. 560. £114·00. Blackwell: Oxford. 1985.

Three editions in 11 years speaks not only of the rapid changes in the field of ocular pathology but also for the acceptability of the earlier editions. Publishers do not perpetuate flops.

To what extent is the latest edition an improvement on its predecessors? From the beginning there has been a conscious emphasis on clinical relevance, and this is now even more evident, which is as it should be in a text designed for ophthalmologists. An intelligent approach to diagnosis and management presupposes an understanding of the causative processes at a tissue level, and the authors are to be congratulated for their efforts in this direction: they have achieved a large measure of success. There is a considerable increase in literature references, although a minority only are actually discussed, and the section dealing with the lens now includes a valuable contribution on intraocular lens implants and their sequelae. The information generally has been updated and reflects current concepts, but in controversial fields there has been a tendency towards caution which has incurred superficiality at times. The description of primary open angle glaucoma is a case in point: 22 lines in a double–coloumn text does not reflect the importance of this condition, and, while it is true to say, as the authors do, that the pathogenesis remains obscure, this is to do less than justice to the large effort which has gone into defining some of the contributory tissue disturbances.

In reviewing a textbook of this size it is impracticable to comment on every topic and I chose to pay particular attention to areas in which I pretend to some expertise, to assess the reliability, and topics which I find confusing, to judge the extent to which the text illuminates them. In respect of the first objective I could find very little with which to take exception, and so far as the second was concerned I was often pleasantly surprised.

At the end of the book there is a self-assessment quiz which can be answered with confidence if the reader has assimilated what has gone before. I was relieved to find that I agreed with virtually all the answers (perhaps a more humble reviewer would say he was relieved not to be shown up).

The illustrations and standard of presentation are excellent, and I applaud the replacement of the well-meaning but inconvenient stereophotographs slotted into the back of the second edition by a fewer number of superb colour plates.

Taken as a whole, this is a book which deserves and can expect to extend the popularity of the earlier editions. I commend it warmly to those for whom it is designed, ophthalmologists with inquiring minds who want to be better informed about the diseases they are called upon to treat. ALEC GARNER

Retinal Detachment: A Colour Manual of Diagnosis and Treatment. By Jack J Kanski. Pp. 161. £29·50. Butterworth: Sevenoaks, Kent. 1986.

The 10 chapters of this book have a fast and punchy presentation characteristic of the author's style. There are numerous helpful lists in the text, which is highlighted by boxed notes and linked by explanatory paragraphs. Although not specifically referred to in the text there are ample end-of-chapter references for further reading. There is an immensely satisfactory index for quick reference.

The book is beautifully laid out and the production is of exceptional quality. The style of presentation is particularly effective in certain parts of the book. Thus I especially liked the section devoted to examination of the retina, where the current principles of technique are very well described. Conversely, in this type of presentation it is sometimes difficult to produce adequate explanation of principles which are going to influence the choice of treatment. For example, although there is description of periretinal membranes, it is hard for the reader to decide how the presence of these membranes, by their effect on the retina to which they are intimately related, affects the management of the retinal detachment. From a purely factual point of view I found that comments about the role of vitrectomy in retinal detachment surgery, aphakic detachment, and uses of intraocular air are unsatisfactory. There are a few inaccuracies—for example, macular tears are exceptionally rare, and snail-track and lattice degeneration are rarely found together.

I think that the use of ultrasonography might have been mentioned, particularly in relationship to its role in the diagnosis and character of retinal detachment when there are opacities in the media of either a transient (e.g., vitreous haemorrhage) or permanent nature (e.g. cataract). The pictures by Tarrant are of a superb standard, although I did not, for example, consider that the illustrations of subretinal fibrosis and traction detachment were typical examples. In the main the colour photographs in the operative section were also excellent. It is nice to see a mention of some of the modern problems confronting the retinal surgeon. For example, there were useful hints on the management of detachment in the presence of intraocular lenses.

All in all this is a splendid book, and it is packed full of gems of knowledge. It is particularly suited for training ophthalmologists reading for an examination and, with its large number of colour illustrations, is very reasonably priced. I thoroughly enjoyed reading it and wholeheartedly recommend all my colleagues to do the same. A H CHIGNELL

An Outline of Ophthalmology. By Roger L Coakes and Patrick J Holmes Sellors. Pp. 195. £7·95. Wright: Bristol. 1985.

This excellent compact book is written principally for medical students and has an interesting symptomatic approach to eye disorders. It contains a large amount of information, very well organised into five principal sections on symptoms and two sections based on the eye in systemic disease and ophthalmic investigations with treatment. Profuse black-and-white illustrations accompany the text.

There are some very valuable sections in the book, and I particularly liked those on optical aids, diagnostic tests, and ocular toxicology and was amused by the list of common misconceptions. (About the only omission here was 'Won't my cataract be removed with the laser-beam?'.) My only criticism is that, whilst most of the photographs are eminently clear, some of them would have been much better in colour.

I would thoroughly recommend this book to all medical students. I think it will find a useful place in most casualty departments and general practices as a quick reference for the diagnosis of eye symptoms, and I am sure it will prove useful to nurses and opticians. RONALD J MARSH

Heredity and Visual Development. Eds. Joel B Sheffield and S Robert Hilfer. Pp. 214. DM 164·00. Springer-Verlag: Berlin. 1985.

The Eighth Symposium on Ocular and Visual Development was devoted to exploring current knowledge on the structural and functional bases of genetic eye diseases, a major objective of these symposia being to foster communication between basic scientist and clinician. Of the eight papers presented here five are on retinal dystrophies, both in animal models and in humans, and review large areas of basic research into this important group of disorders. The papers by Bolton and Marshall and by Ripps and his colleagues can be particularly recommended.

Melanin in the fetal retinal pigment epithelium probably determines the chiasmatic pathway choice made by growing axons; hence the abnormality seen in animal and human albinos. Studies of the early development of central visual pathways in normal and albino ferrets support this hypothesis.

Recombinant DNA technology was used to study hereditary cataract in animal models, which may be associated with a reduction or absence of a specific crystallin, while monoclonal antibodies were used to identify the unusual glycoprotein in the cornea of patients with Groenouw's macular dystrophy.

This is an interesting group of review articles by basic scientists who have made an appreciable attempt to be understood by clinicians. It would be a great pity if clinicians do not make the effort required to read them. BARRIE JAY

Genetics of Ocular Disease, Acute Retinal Necrosis Syndrome, Phthisis bulbi. Edited by W Straub. Pp. 164. SFr. 129. Karger: Basel. 1985.

This is the tenth volume in the series 'Developments in Ophthalmology' and contains three monographs on widely different topics. The late Jules François discusses the complex subject of multifactorial inheritance, and then considers its relevance to several groups of disorders, including glaucoma and strabismus. Certain of his conclusions must remain open to question, but they do indicate areas where further research is necessary.

Hayreh presents four cases of acute retinal necrosis and reviews 74 cases in the literature. In discussing the pathogenesis of the condition he concludes that, despite suggestions of a viral aetiology, this still remains unknown. The disease appears to represent an acute ocular panvasculitis, a term that Hayreh prefers to acute retinal necrosis.

From his experience of studying the histopathology of 74 eyes Stefani concludes that phthisis bulbi, which is usually post-traumatic, results from pathological processes associated with wound healing. Intraocular haemorrhage is an important predisposing event, and this observation is relevant in the management of severe ocular trauma.

It is useful to have these review articles available for reference. BARRIE JAY

Manifestations Ophtalmologiques des Parasitoses. By J S DIALLO. Pp. 358. 450F. Masson: Paris. 1985.

The Société Française d'Ophtalmologie provides a valuable service to French reading ophthalmologists by producing each year a report on one particular topic. This volume covers a vast subject succinctly, has a useful bibliography, particularly of papers in French, and can be recommended as a useful reference book. BARRIE JAY

Notes

Finance offered

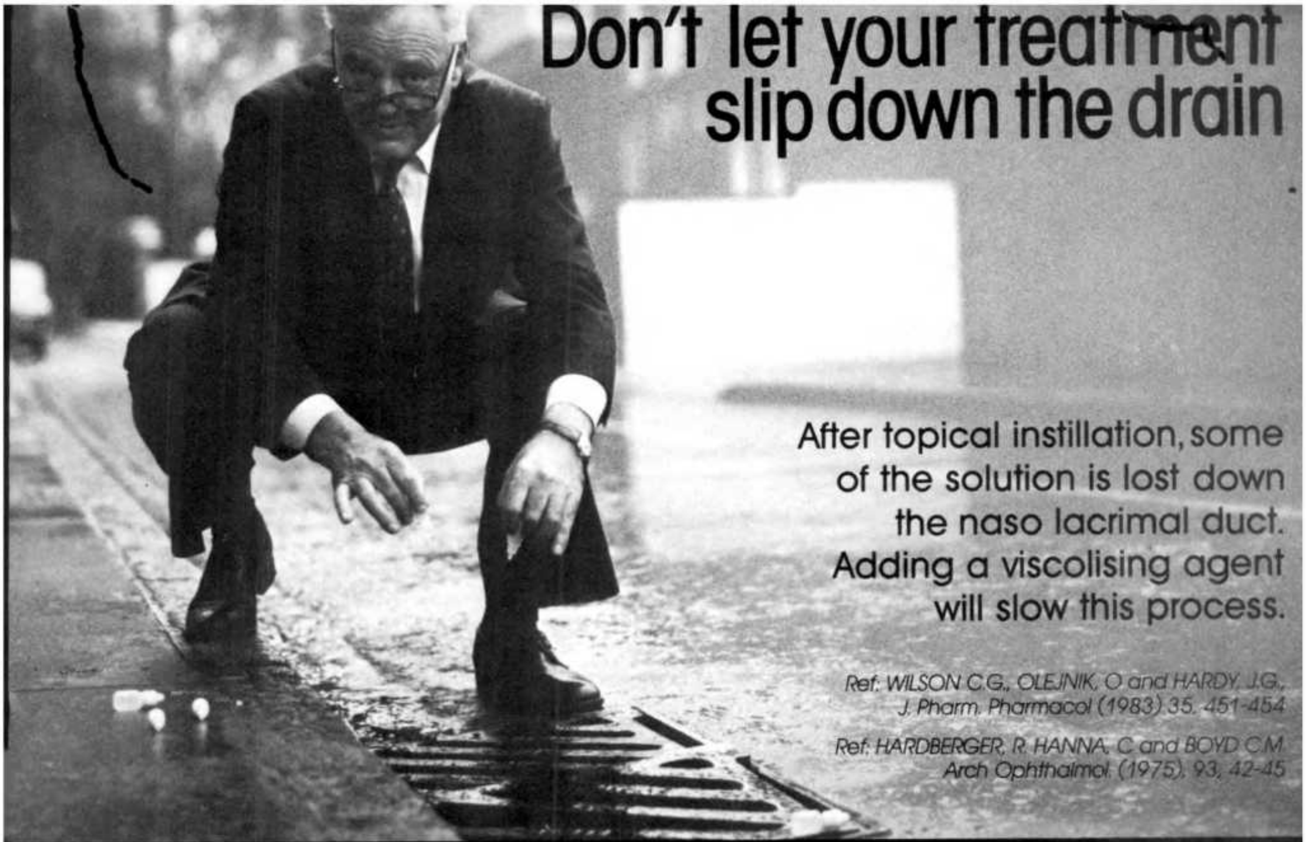
David Cole Travel Fellowship
The David Cole Travel fellowship, instituted by Merck Sharp and Dohme in memory of Professor David Cole, will assist a visit to a hospital or research centre during the academic year starting 1 October 1987. The award will be equivalent to £2000. The purpose of the award is to enable the successful applicant to gain experience and knowledge in pursuit of a specific project related to glaucoma.

Glaucoma Group Research Grant
The Glaucoma Group Research Grant, sponsored by International Glaucoma Association, will be available for a research project clinically orientated towards glaucoma for 1987. The award will be equivalent to £2000. The Grant may be used towards salary or project expenses or for buying equipment.

Both these awards are available to medical graduates and non-medical scientists resident in the United Kingdom or the Irish Republic. They may be held concurrently with other awards. Further details and application forms from Dr S Nagasubramanian, Secretary Glaucoma Group, Glaucoma Unit, Moorfields Eye Hospital, High Holborn, London WC1V 7AN. The closing date for applications is 19 June 1987. The successful candidate will be informed by August 1987.

Ophthalmic pathology meeting

Every five years the European Ophthalmic Pathology Society and the Verhoeff Society of the USA unite for a combined meeting. The venue on 20-24th April 1986 was Philadelphia, with Drs M Yanoff and W Frayer of the Scheie Eye Institute acting as the hosts. Cases with clinicopathological correlation were presented by each of the participants as listed: Hereditary olivopontocerebellar atrophy (P Naeser, Sweden). Aicardi's syndrome (R Font, USA). Orbitofacial and ocular neurofibromatosis (F Weber, Switzerland). Niemann-Pick variant: type c (D Cogan and T Kuwabara, USA). Dysgenetic glaucoma (M Quintana, Spain). Choroidal melanoma after ruthenium irradiation (W Manschot, Netherlands). Dysplastic naevus syndrome in an infant (O Jensen, Denmark). Lattice corneal dystrophy: type 3 (G Klintworth, USA). Reis-Buckler dystrophy (W Spencer, USA). Lipidisation and detachment of the RPE (W Green, USA). Ridley lens (D Apple, USA). Mycobacterial keratitis in radial keratotomy (N Rao, USA). Perforating fungal corneal ulcer (V Curtin, USA). Intraocular coccidioidomycosis (R Foos, USA). Nocardia endophthalmitis (A Ferry, USA). Neuronal intranuclear inclusion disease (A Tarkkanen, Finland). Serpiginous choroiditis (D Gass, USA). Stevens-Johnson syndrome (J Prause, Denmark). Vogt-Koyanagi-Harada syndrome (F Winter, USA). Necrogranulomatous scleritis (E Landolt, Switzerland). Scleritis with rheumatoid arthritis (P Egbert, USA). Eyelid malakophakia (W Frayer, USA). Prosthesiogenic conjunctival carcinoma (G Goder, GDR). Papillary squamous cell carcinoma of lacrimal sac (M Reeh, USA). Sebaceous carcinoma (I McLean, USA). Eyelid malignant syringoma (E Howes, USA). Anterior segment metastasis (H Kirk, USA). Ligneous conjunctivitis (J McGavic, USA). Metastatic breast carcinoma (F Jakobiec, USA). Malignant oculocerebral lymphoma (B Daicker, Switzerland). Eyewall resection of choroidal melanoma (W Lee, UK). Choroidal melanoma (M Yanoff, USA). Iatrogenic extension of uveal melanoma (G Naumann, FRG). Bilateral ocular melanoma (B Crawford, USA). Aneurysmal bone cyst (M Smith, USA). Orbital intraosseous cavernous haemangioma (M Bonink, USA). Orbital alveolar soft parts sarcoma (M Brihaye, Belgium). Orbital plasmacytic tumour (E Kock, Sweden). Proptosis in acute lymphocytic leukaemia (L Zimmerman, USA). Orbital acute monocytic leukaemia (B Streatan, USA). Ocular malignant fibrous histiocytoma (M Vogel, FRG). Orbital malignant fibrous histiocytoma (H Witschel, FRG). Congenital retinoblastoma (R Eagle, USA). An unusual retinoblastoma (A Garner, UK). Pseudoretinoblastoma (A Hamburg, Netherlands). Norrie's disease (D Albert, USA). Medulloblastoma of the pineal gland (T Makley, USA). Although it is not the practice to publish the proceedings, interested persons are invited to contact the individual contributors for further information regarding their cases. In all some 11 countries were represented, and at the official dinner Professor A Tarkkanen, in his capacity as President of the European Society, presented an engraved silver plaque to the American hosts.



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Ref. WILSON C.G., OLEJNIK, O and HARDY, J.G., J. Pharm. Pharmacol (1983) 35, 451-454

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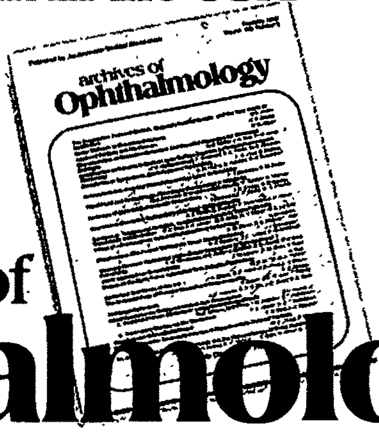

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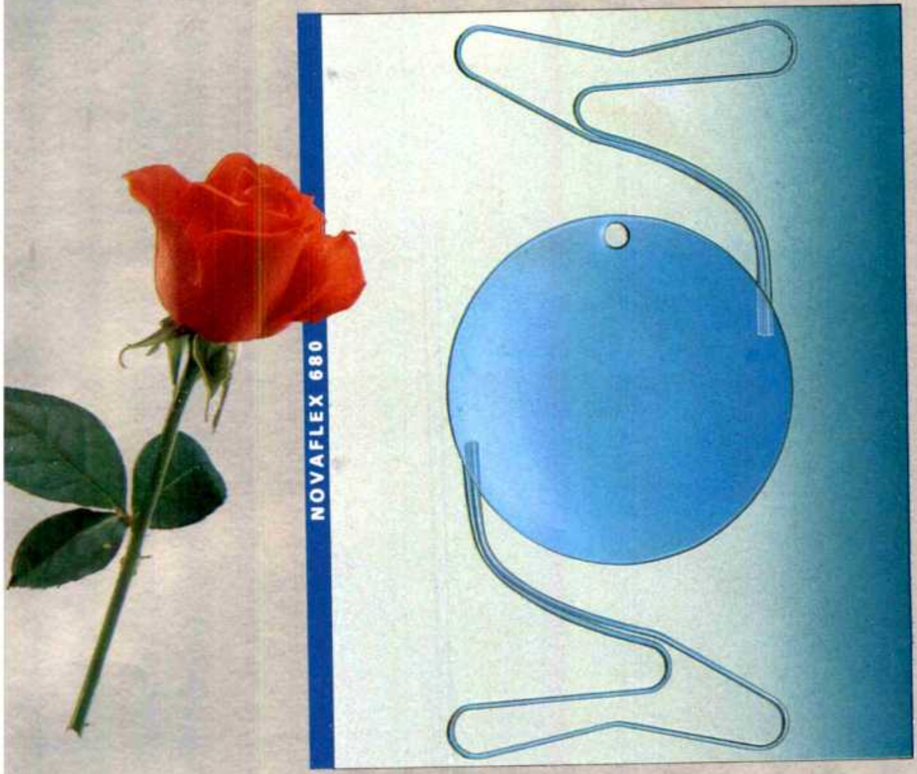

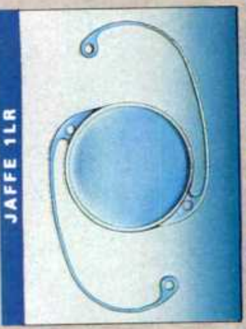

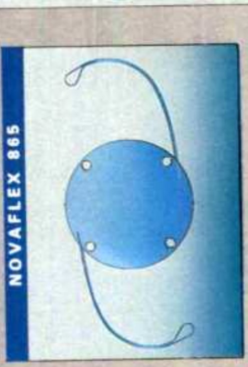

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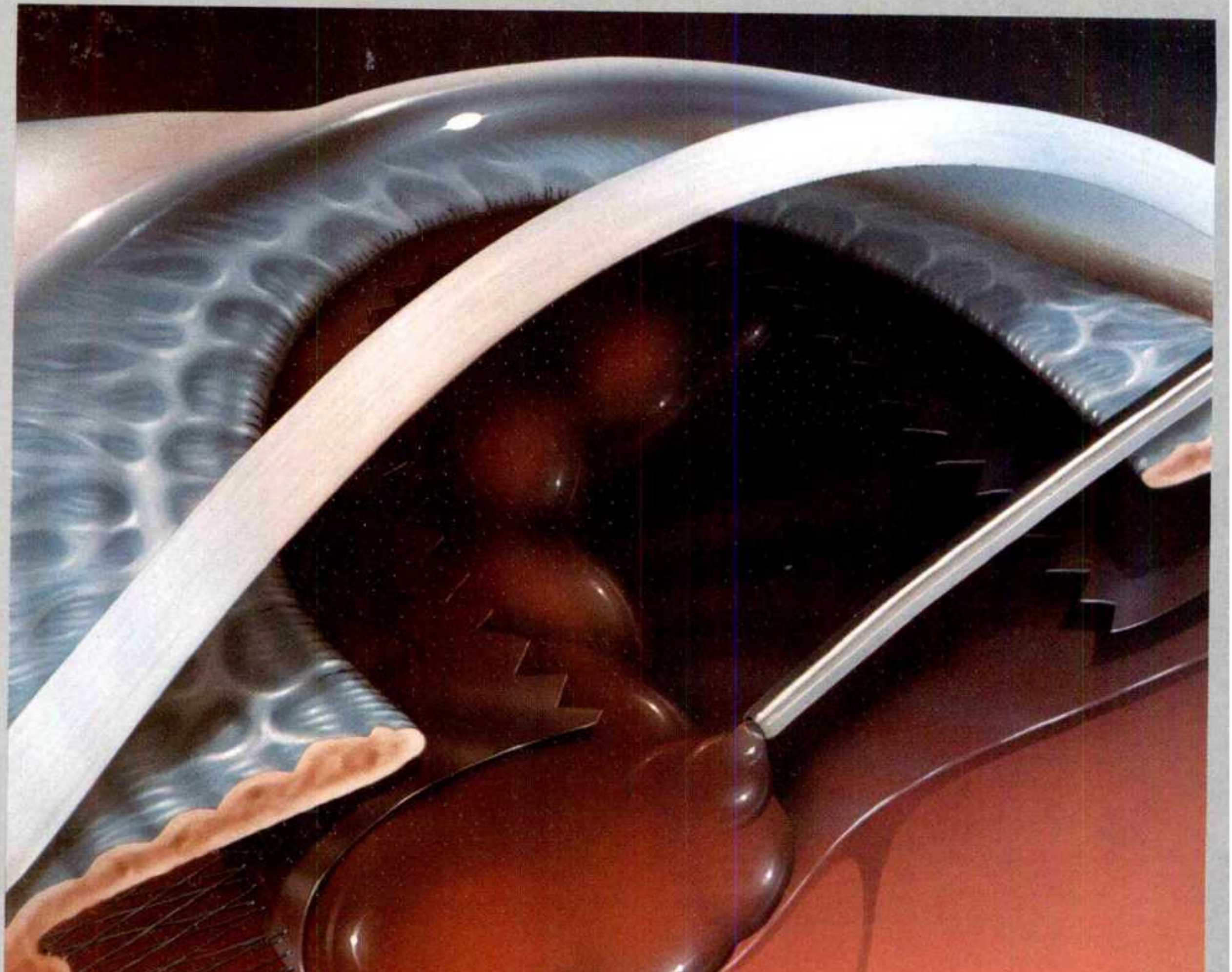

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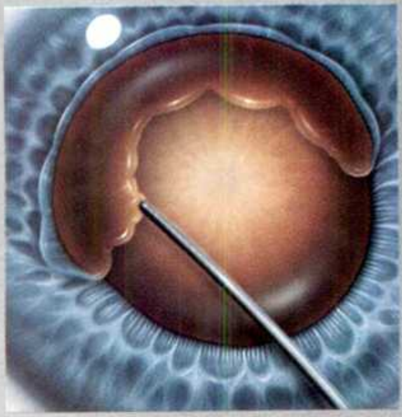

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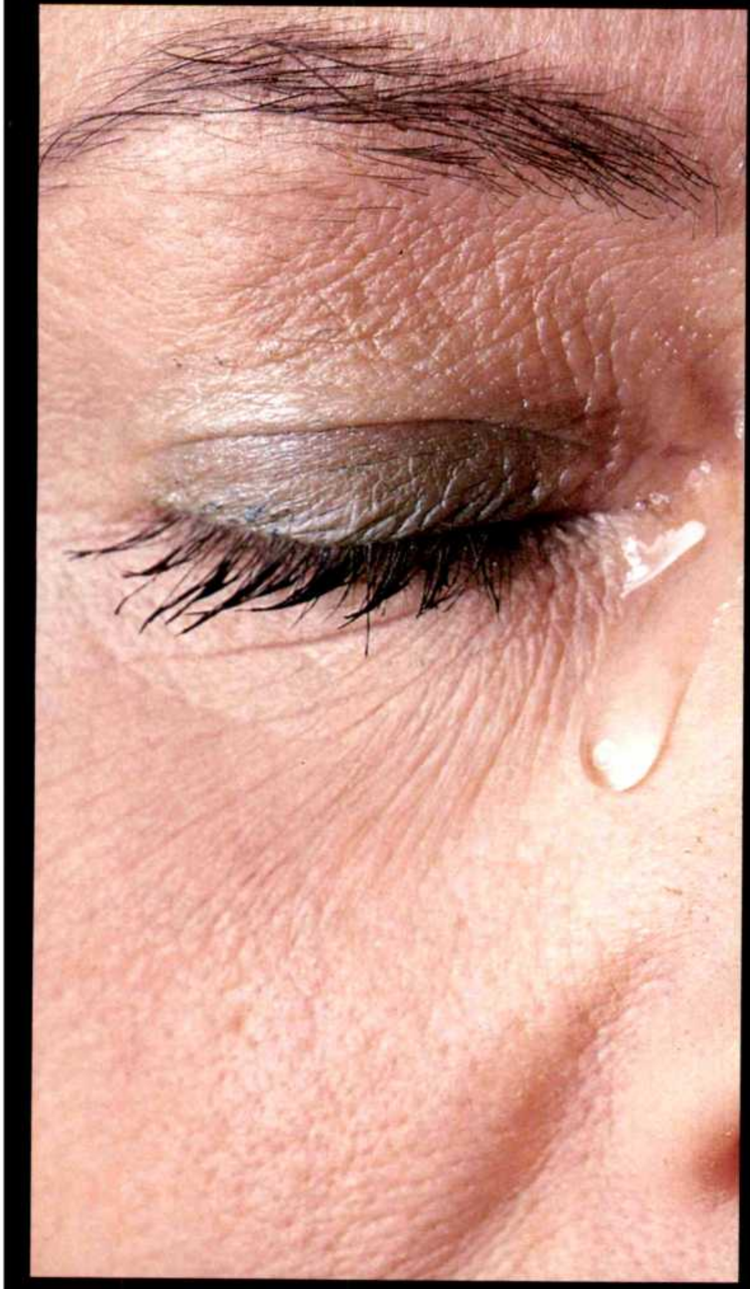

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Cataract: the relation between myopia and cataract morphology

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SUMMARY The association between high myopia and cataract is already well established and an association between simple myopia and cataract has been suggested, but it has not been clear to what extent the myopia precedes the cataract or is the result of it. The present study compares the refraction of a group of 100 British patients at the time of first presentation with cataract in whom the refraction was also known four years previously, with a group of matched controls in whom the refraction was also known four years previous to presentation. The study shows that simple myopia does not appear to predispose to cataract. It is the development of the cataract itself, in particular nuclear sclerosis, which causes the refractive change towards myopia. The myopic change precedes the development of cataract, and patients over the age of 55 showing a myopic change in refraction have a very high probability of developing nuclear sclerotic cataract. The healthy aging eye and eyes with cortical cataract or subcapsular cataract, but without nuclear sclerosis, continue to show a gradual hypermetropic change with time.

The relationship of cataract to high (or degenerative) myopia is a well accepted concept.[1] It has also been considered that this relationship may extend to involve simple myopia and attention has been focused on this recently by Weale,[2] Perkins,[3] and Von Kluxen,[4] who each examined the refractive state of patients presenting at hospital with cataract and found an excess incidence of myopic refraction in them. Racz *et al*,[5] who examined patients with presenile cataract coming to surgery, found an excess incidence of myopia; the –19 to –21 dioptre group being well represented, which further confirms the association of cataract with the higher degrees of myopia.

Nuclear sclerotic cataract itself causes a change towards myopia, and so it is not possible to draw conclusions from these previous studies about the basic refractive states of the patients prior to the development of cataract. It is the object of the present study to make a contribution in this field.

Material and methods

It was decided to study a minimum of 100 patients presenting with cataract, in whom the refraction was known four years prior to the development of cataract, and to compare them with the same number of controls, matched for age, in whom the refraction was also known four years prior to the time of presentation. A period longer than four years would have been preferred but would have severely limited recruitment.

The patients with cataract and the controls were all patients attending a central London ophthalmic practice, with the expectation of a refractive examination and unaware of any eye disease. Only Caucasian subjects resident in England were accepted, in order to exclude the effects of differing environments. They could be admitted to the study if they had already attended four years previously. Patients were assigned to the cataract group when they had cataract visible by slit-lamp examination in the undilated pupil and at least minimal interference with visual acuity 6/7·5 or worse after refractive correction. It was decided to exclude high myopia and a limit was set at −12 D. Patients and controls were excluded if they had a recognised potential cause of cataract, including diabetes. Both the patients and controls were recruited strictly in order of their presentation without the exclusion of any cases that satisfied the above criteria. No attempt was made to match patients and controls for sex, but a

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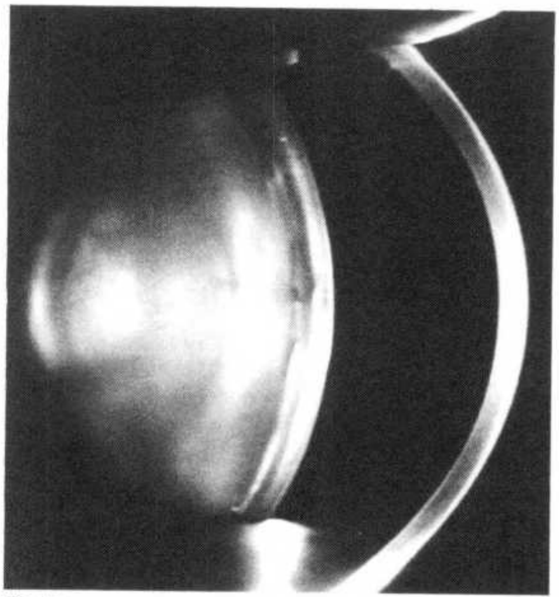


Fig. 1a

Fig. 1 *Slit-image photography of lenses with early cataract.* (a) *Cortical,* (b) *nuclear, and* (c) *subcapsular.*

good match occurred spontaneously. The cataract group consisted of 110 patients, 71 female and 39 male, with 203 affected eyes. There were 110 controls (220 eyes), 74 female and 36 male.

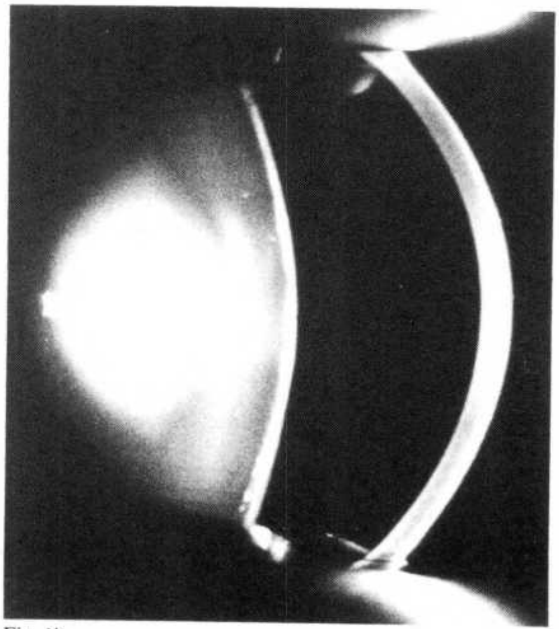


Fig. 1b

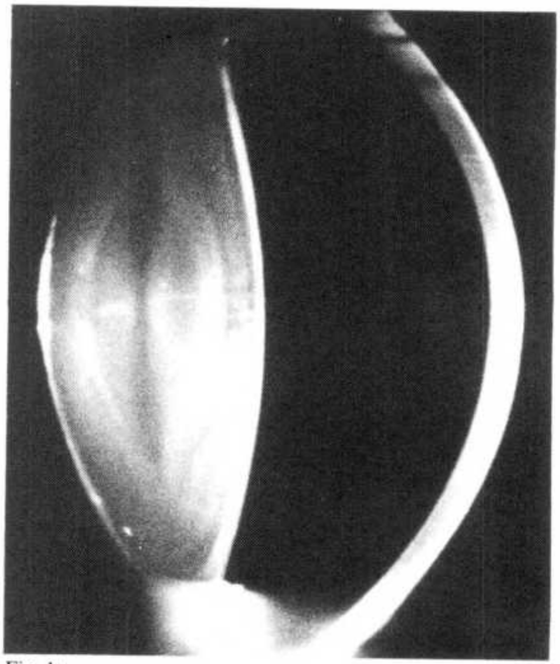


Fig. 1c

The refractions were recorded, and to facilitate analysis they were simplified to spherical equivalent to the nearest 0·125 dioptres (ie., spherical component plus half cylindrical power in dioptres). By comparing the refraction at the time of presentation with cataract with the refraction four years previously the change in refraction could be determined. To simplify the tabulation of the results in respect of age the subjects were grouped into five-year age categories.

The cataracts were classified at the slit-lamp into cortical, nuclear, and subcapsular (Figs. 1a, b, and c). Although more than one cataract type may be present in an eye, it is possible to assess the refractive change associated with each cataract type separately or in combination by grouping the data as in Fig. 2. By this means it is possible to partition the data in a number of ways, either by using mutually exclusive categories or, for example, by comparing all cataracts having nuclear sclerosis against those without nuclear sclerosis.

Results

The age distributions of patients presenting with cataract and the matched control group are shown in Fig 3, from which it will be noted there is very close agreement. The most frequent age of presentation for both sample population was between 71-75 years. In patients older than this the prevalence of cataract

Grouping of cataract types for analysis

		Subcapsular Cataract	
		Present	Absent
Nuclear	Present	a	b
Cataract	Absent	c	d

a comprises (N + SC) and (N + SC + C)
b " (N) and (N + C)
c " (SC) and (SC + C)
d " (C alone)

where N = Nuclear sclerosis
SC = Subcapsular cataract
C = Cortical cataract

eg (N + SC) represents the simultaneous presence of nuclear sclerosis and subcapsular cataract

Fig. 2 *Contingency matrix for grouping the data according to the presence or absence of both nuclear and subcapsular cataract.*

was of course higher, but the incidence of presentation of new cases declined.

The incidence of the various types of cataract as a function of age is shown in Fig. 4. Among those eyes presenting with cataract cortical opacities were the most common, occurring in 63% of eyes, with nuclear cataract in 41% and subcapsular cataract in 24%.

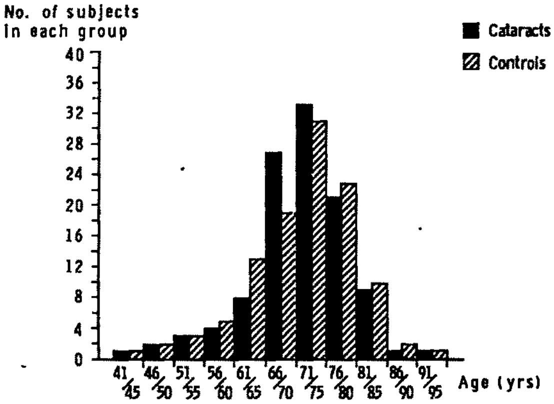


Fig. 3 *Age distribution of all cataract patients (n=110) and non cataractous controls (n=110).*

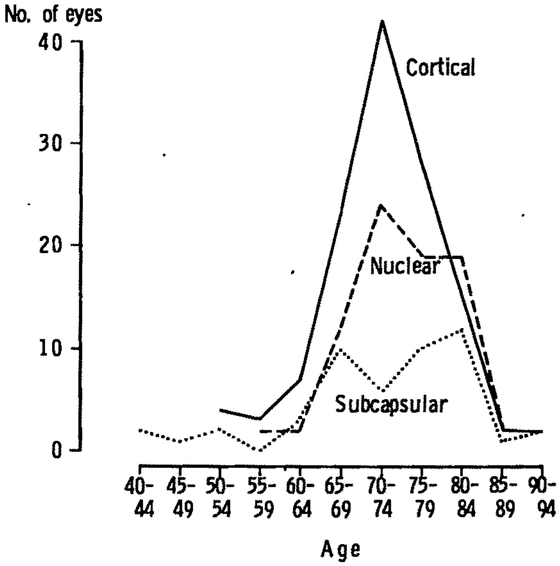


Fig. 4 *Incidence of the various types of cataract, as a function of refractive error (all eyes). In 55 of the 202 eyes presenting with cataract more than one morphological type of lens opacity was present (see Table 1).*

Slightly more than 70% of all eyes with cataract showed a single type of cataract. The frequencies of these mutually exclusive cataracts and their occurrence in combination are given in Table 1. The incidence of the different cataracts occurring singly or in combination is significantly different from chance, (χ^2 RE = 92·91, and χ^2 LE = 91·98, for df=6 have probabilities of occurrence of $p < 0{\cdot}0001$). A high correlation of cataract types occurring in the right and left eyes is also evident from Table 1, there being only a small number of uniocular cataracts. Such a high positive intereye correlation accords with clinical experience and is present in most ophthalmic data.[6,7] It precludes the combining of observations from right and left eyes for a single statistical analysis. Separate analysis have therefore been conducted on

Table 1 *Frequencies of the different cataract types presenting in isolation or in combination for right and left eyes*

Cataract combination	*Right*	*Left*
Cortical alone (C)	46	46
Nuclear alone (N)	19	16
Subcapsular alone (SC)	10	10
C with N	13	13
C with SC	3	4
N with SC	9	9
C with N with SC	2	2
Totals	102	100

These frequencies are from a total of 110 patients presenting with cataract, of which 18 were uniocular (10 right and 8 left).

Table 2 *Frequencies of the four major cataract groups as defined in Fig. 2*

	Right eye		*Left eye*	
	Subscapsular present	*Cataract absent*	*Subcapsular present*	*Cataract absent*
Nuclear present	11	32	11	29
Cataract present	13	46	14	46

single-eye data in a two-eye design, and only those results where the analyses gave consistent findings for right and left eyes are presented.

To test several hypotheses on the role of nuclear cataract and subcapsular cataract on refractive change over time the data were reorganised into four mutually exclusive cataract groups as defined in Fig. 2. This four-way grouping permits a comparison of the presence and absence of either nuclear cataract or subcapsular cataract or both. It will be appreciated from this grouping that the presence of cortical cataract is treated as a random variable, though since all the data treated in this way are from the eyes with cataracts those coded into cell D of the contingency table refer to the presence of cortical cataract alone. When organised in this way, the separate data for right and left eyes are as shown in Table 2. Analyses by χ^2 on the data for both right and left eyes show there was no difference in the presence or absence of nuclear cataract in the proportion of eyes presenting either with or without subcapsular cataract, (χ^2 RE = 0·033, χ^2 LE = 0·056, with df=1). At its time of initial occurrence, therefore, the presence of nuclear sclerosis was unrelated to the presence of subcapsular cataract.

The mean refractive error (spherical equivalent) for the four different cataract categories and the control group, both at presentation and four years prior to presentation, are shown in Table 3. The mean refraction of the controls at the initial examination was one of slight hypermetropia (R+0·90 D and L+0·72 D to the nearest 0·01 D), which accords closely with the most commonly occurring refractive error in the general population found by many other investigators.[8] The distributions of refractive errors for all cataract patients and controls both at the time of first cataract presentation and four years previously are shown in Figs. 5a, b, c, d. It will be seen that there was very close agreement between the two samples at four years prior to cataract presentation. Although the distribution of refractive errors departed slightly from normality (ie., a leptokurtosis with slight skewness towards myopia), this was not sufficient in the present samples to invalidate the use of parametric variance analyses.

However, the small sample size and related high variance of some of the cataract categories (notably C) precludes a useful analysis of the data as presented in Table 3. For example, the negative mean refraction of the subcapsular group (C) at both examination times is due almost entirely to the occurrence of one patient with bilateral high myopia as detailed in the footnote to Table 3. Nevertheless, all analyses presented in this paper include this myopic case,

Table 3 *Mean refraction (spherical equivalent in dioptres) among the different cataract categories**

Cataract Group‡		*(I) Four years preceding presentation*		*(II) At 'cataract' presentation*		*(III) Refractive change†*	
		RE	*LE*	*RE*	*LE*	*RE*	*LE*
A	$\bar{x}$	0·975	1·102	−0·750	−0·523	−1·725	−1·625
	sd	2·071	1·904	2·391	2·404	0·914	1·169
B	$\bar{x}$	0·277	0·405	−1·121	−0·832	−1·398	−1·237
	sd	2·690	2·760	2·977	2·938	1·086	0·841
C§	$\bar{x}$	−1·886	−1·179	−1·705	−1·036	0·182	0·143
	sd	4·568	3·686	4·365	3·602	0·459	0·373
D	$\bar{x}$	0·639	0·723	0·859	0·937	0·220	0·215
	sd	1·909	1·794	1·975	1·826	0·416	0·438
Controls	$\bar{x}$	0·902	0·717	1·050	0·850	0·147	0·133
	sd	2·184	2·359	2·255	2·360	0·392	0·395

* For definition of cataract group see Fig 2.

† The computed mean values and standard deviations for 'refractive change' (ie., 'presentation' minus 'prior') are based on individual differences for all patients. Consequently, where the mean 'refractive change' does not exactly correspond with the difference between the means for 'presentation' and 'prior' refractive states this is a result of variance in the data.

‡ For details of the number of eyes in each group see Table 1, where $\bar{x}$ = mean and SD = standard deviation.

§ If one high myopic case (R −11·625, L −11·00 at four years preceding cataract and R −11·00, R −10·625 at the presentation of cataract) is excluded from this group, the mean refractions and corresponding SD values for group C revise to: $\bar{x}$: (I) R −0·739, L −0·423 (SD: 2·989, 2·409); (II) R −0·573, L −0·298 (SD 3·197, 2·462); (III) R +0·167, L +0·125 (SD 0·441, 0·382).

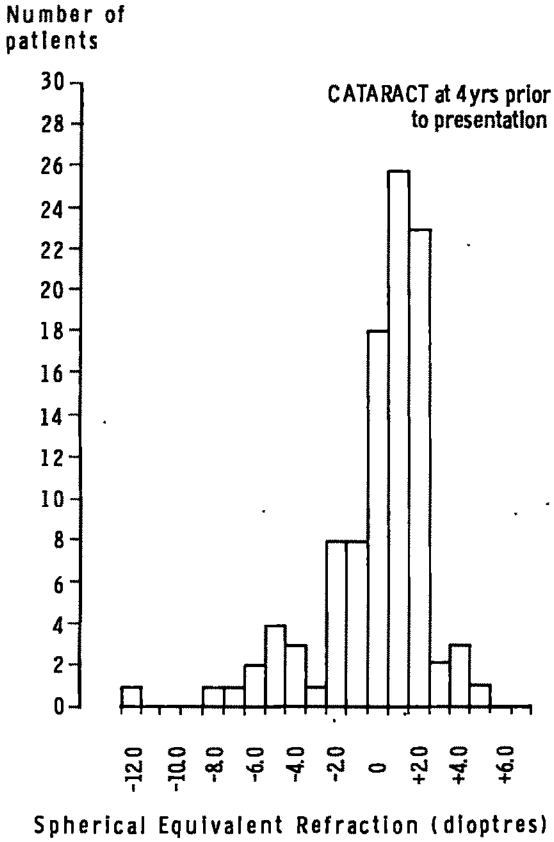


Fig. 5a

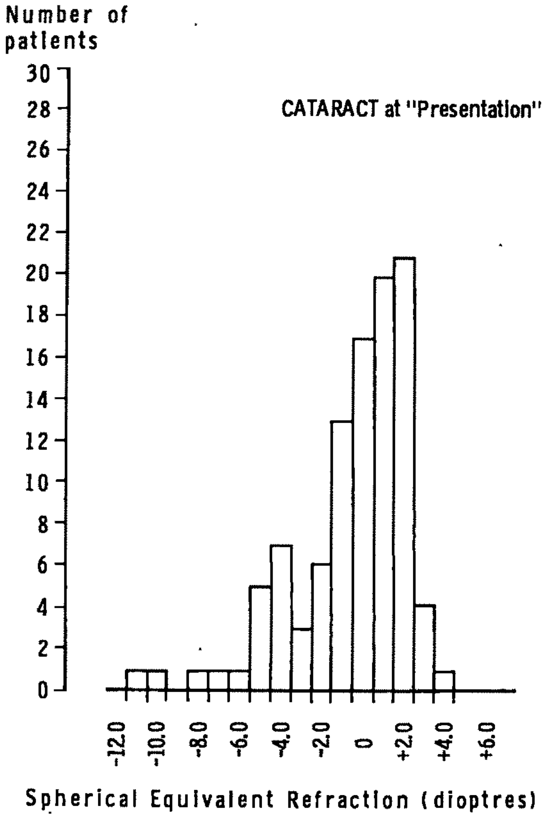


Fig. 5b

Fig. 5 *Distribution of refractive errors for 110 cataract patients* (a) *four years prior to the presentation of cataract and* (b) *at the time of initial cataract presentation; compared with the distribution of refractive errors for 110 age matched controls* (c) *four years prior to presentation and* (d) *at time of presentation for a refractive examination. Right eye data.**

since it did not exceed the exclusion criteria established at the outset of the study. Consequently, to test the hypothesis that nuclear cataract is associated with a myopic shift over time, the cataract data were regrouped into two categories at presentation comprising all those eyes possessing nuclear cataract versus all eyes without nuclear cataract. The mean refractions for these regrouped data are shown in Table 4. The analysis of variance for right eye data is summarised in Table 5. It shows a highly significant different change of refraction over four years in the nuclear compared with non nuclear cataract groups and controls. This interaction term is due to a relatively large mean myopic change in the presence of nuclear cataract (R −1·47 D, L −1·34 D), whereas there is a slight hypermetropic change both in the non-nuclear cataract group and in controls. A post-hoc Newman-Keuls test shows the change in refraction over four years in each of the three groups (i.e., nuclear cataract, non-nuclear cataract, and control) to be highly significant, as also were the differences in mean refraction between cataract categories and controls at each examination time ($p < 0{\cdot}01$). (The differences between mean refractions at four years prior to cataract presentation become insignificant if the single case of high myopia is removed. For details of this case see footnote to Table 3.) The distribution of the change in refractive error over time for the nuclear and non-nuclear cataract groups is shown in Figs. 6 a, b.

To test the hypothesis that the myopic shift occurring in nuclear cataract is independent of the initial ametropic state the data were structured for further analysis according to whether an eye was myopic or hypermetropic at four years prior to cataract presentation. Separate analyses of variance on right and left eye data were conducted on the *change* in refractive error occurring over the four-year interval between examinations. A summary of the variance analysis for right eye data is given in Table 6, from which it

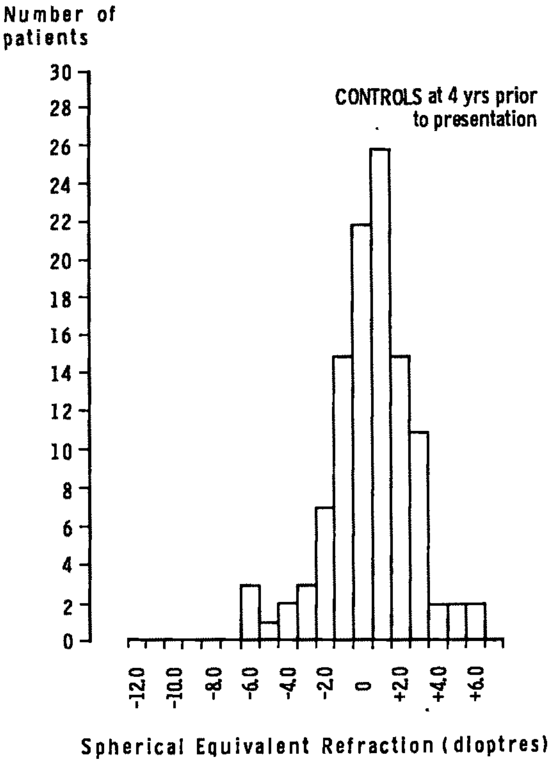


Fig. 5c

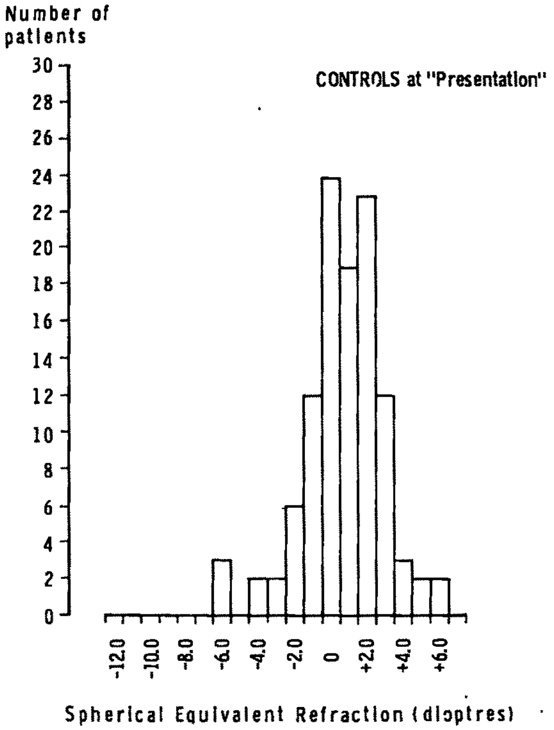


Fig. 5d

will be seen that there was neither a significant interaction of refractive change between ametropia and cataract type, nor was there a significant main effect due to ametropic state. This implies that the mean refraction for the sample of myopes and the sample of hypermetropes did not differ between the cataract group and the controls. The data were examined further to determine whether there was a greater proportion of myopes than of non-myopes in the cataract group at four years prior to presentation. Table 7 shows there was no difference between the cataract group and controls in the proportion of myopes to non-myopes. A χ^2 test gives the probability associated with these proportions being the same in each group as p>0·8, (χ^2 RE=0·028, and χ^2 LE=0·058, each with df=1). The myopic shift observed in nuclear cataract was therefore independent of whether an eye started out as being refractively myopic or hypermetropic.

Analyses of variance conducted on the data when

Table 4 *Mean refraction error (spherical equivalent in dioptres) for eyes with and without nuclear cataract*

*Cataract Group**		*(I) Four years preceding presentation*		*(II) At 'cataract' presentation*		*(III) Refractive change† (II – I)*	
		RE	*LE*	*RE*	*LE*	*RE*	*LE*
(A+B) nuclear cataract	$\bar{x}$	0·439	0·597	−1·035	−0·747	−1·474	−1·344
	sd	2·554	2·549	2·828	2·775	1·048	0·943
(C+D) non–nuclear cataract	$\bar{x}$	0·168	0·279	0·381	0·477	0·213	0·198
	sd	2·745	2·471	2·731	2·472	0·421	0·422
Controls	$\bar{x}$	0·902	0·717	1·050	0·850	0·147	0·133
	sd	2·184	2·359	2·255	2·360	0·392	0·395

* and † see footnotes to Table 3.

Table 5 *Summary analysis of variance of refractive error as a function of examination time (presentation versus four years prior) and cataract group (nuclear versus non-nuclear versus controls). Right eye data**

Source of variation	*SS*	*DF*	*F*	*p*
Cataract group (C)	110·36	2	4·58	0·0113
Error	2517·08	209		
Examination time (T)	12·57	1	71·85	<0·0001
C × T	46·41	2	132·60	<0·0001
Error	36·58	209		

* Anova for left eye shows similar results with a comparable distribution of variances.

Table 6 *Summary analysis of variance of four-year change in refraction as a function of initial ametropic state (myopia versus hypermetropia) and cataract group (nuclear versus non-nuclear versus controls). Right eye data**

Source of variation	*SS*	*DF*	*F*	*p*
Ametropia (A)	0·1691	1	0·49	0·4845
Cataract group (C)	87·2405	2	126·53	<0·0001
A × C	1·4768	2	2·14	0·1201
Error	71·0185	206		

* Anova for left eye shows similar results with a comparable distribution of variances.

grouped according to the patients' sex showed there to be no difference in the refractive change in the nuclear and non-nuclear cataract groups for males compared with females.

Discussion

The application of the findings of this study, may be limited by the restrictive nature of the sampling, which has been confined to a group of Caucasian British patients attending a central London practice. However, this is a good place in which to make a study of the relationship of simple myopia to cataract since environmental factors in the causation of cataract are minimal.

The finding of an excess incidence of cataract in the female is similar to that found by Perkins.[3] It is interesting that the same ratio of female to male occurs in the controls. Although the study deals with age groups in which females predominate, since the sex ratio is the same in the cataract group and in the controls it cannot be stated that the female is more prone to cataract.

The present study differs from previous studies in that the refractive state of eyes were obtained at the time of *first* presentation with cataract and compared with the refractive state of these same eyes before the

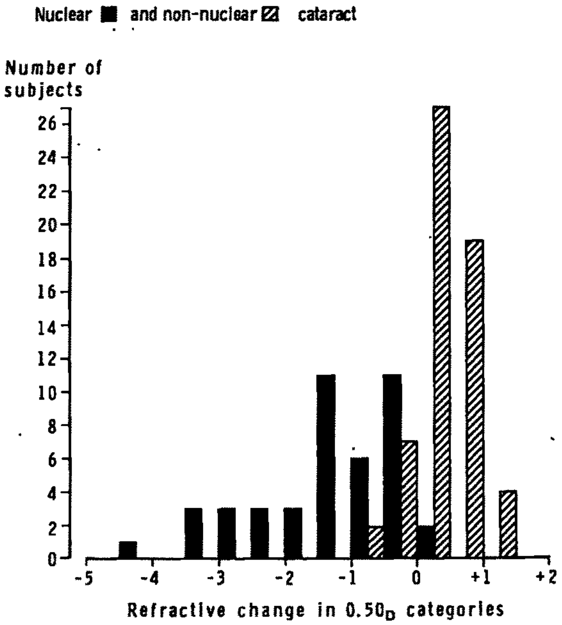


Fig. 6a

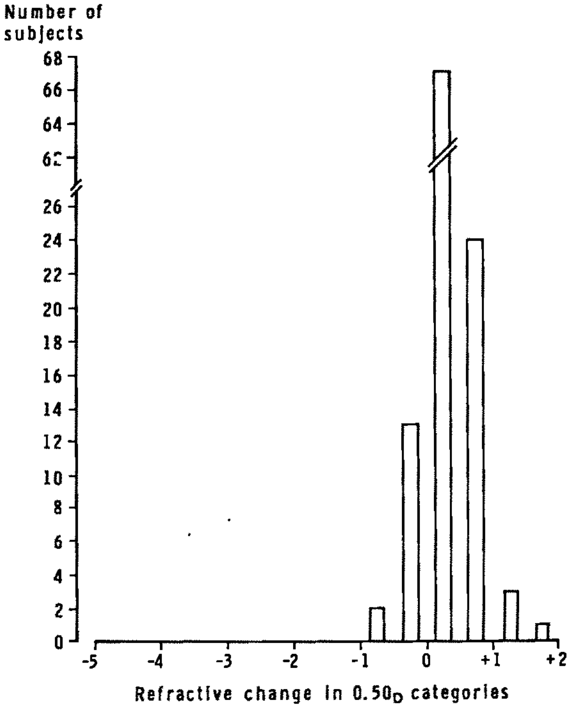


Fig. 6b

Fig. 6 *Refractive change over four years of eyes with* (a) *nuclear cataract and non-nuclear cataract and* (b) *controls (right eye data).*

Table 7 *Frequency of patients having myopia and those without myopia (ie., emmetropia and hypermetropia) at four years prior to presentation, for the cataract group and the controls. Right eye data*

	Right eye		*Left eye*	
	Cataract group	*Controls*	*Cataract group*	*Controls*
Myopes	29	30	26	27
Non-myopes	73	80	74	83
Ratio myopes/ non-myopes	0·397	0·375	0·351	0·325

development of cataract. The cataracts were seen at the time of their first presentation. They can therefore be presumed to be earlier in their natural history than would be the case in those patients being examined at hospital after referral with cataract, as have been considered in other studies.

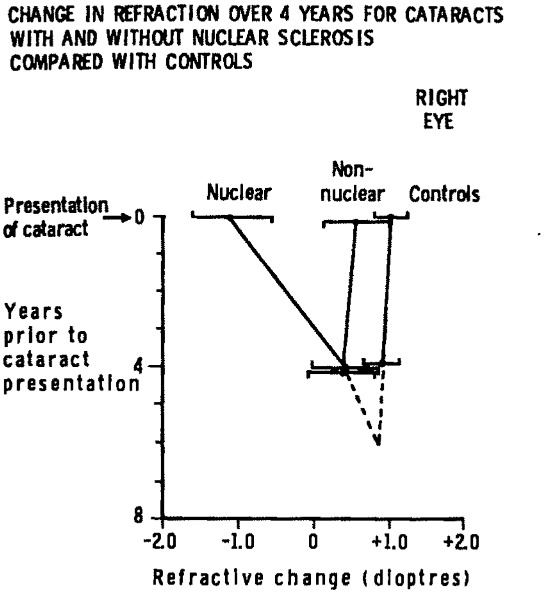
A tendency to myopia was confirmed at the time of diagnosis of cataract, which corroborates the work of Weale,[2] Perkins,[3] Von Kluxen.[4] In particular, it is shown that a marked myopic shift (Fig. 5) had occurred in the four years preceding the presentation of cataract only in those eyes with nuclear cataract. Furthermore, there is no evidence in the data that the myopic shift is any different among eyes which were myopic or hypermetropic before the presentation with cataract. From these results it is possible to speculate that the increased prevalence of myopia among eyes with cataract is entirely due to the cataract and did not precede it. This is further substantiated by the extremely close agreement of mean refractive error between the cataract group and controls at the four-year stage preceding cataract presentation.

When the mean refractions for both ophthalmic examinations for the cataracts and the controls are plotted graphically (Fig. 7), it can be seen that they represent two diverging groups of individuals.

By the application of Darwinian theory[9] it can be suggested that each group has evolved from one common group of individuals, which is shown in the graph by the extrapolated dotted line. It is reasonable to conclude, therefore, that simple myopia does not predispose to cataract, but is the product of cataracts which include the element of nuclear sclerosis.

There is also a suggestion in the data that the combination of nuclear and subcapsular cataract (group A) produces the largest refractive change, (R −1·725 D, L −1·625 D in four years; Table 4). Although this is not significantly different from the effects of nuclear cataract alone, it has been noted previously[10] that lenses with nuclear sclerosis and subcapsular cataract are liable to have a thinned cortex, with reduced radius of curvature of the anterior surface, so that a greater change in this group may be explained by the combination of refractive index change (nuclear) and curvature change (cortical).

The relation of hypermetropia to cataract has been considered by Bourdon-Cooper,[11] who observed that cataract was more common in ametropia, especially in hypermetropia. The contrary was reported by Von Kluxen,[4] who found cataract to be common in myopia and emmetropia but rare in hypermetropia. In the present study, which used a random sampling procedure for the inclusion of all eligible patients at the time of first presentation with cataract, there was no evidence from the refractions of four years previously (when cataract was not present) that myopia or hypermetropia were more prevalent than among a sample of age matched non cataractous controls. Hence, excluding the special condition of the degenerative myopias in excess of −10·00 D, a



Horizontal bars indicate ± 1 SEM

Note: the values for the non-nuclear cataracts are the corrected means following the removal of the high myopic case

Fig. 7 *The change in refraction with time for eyes with nuclear cataract and non-cataractous eyes (right eye data). The broken line is extrapolated to a proposed common mean refractive status prior to the onset of cataractous changes, which, it is suggested, occur at about six years before the clinical appearance of a cataract by slit-lamp examination. The horizontal bars indicate ±1 standard error of the mean. The mean values for the non-nuclear cataracts exclude the case of high myopia (see footnote to Table 4).*

refractively myopic eye is at no greater risk of developing cataract than one with hypermetropia.

It has been suggested that stress induced in the lens fibres by the change in the shape of the lens on accommodation is a cause of cataract. Bourden-Cooper[11] suggested that the greater need to accommodate by the hypermetropic eye might be causative. The theory of accommodative cause can alternatively be applied to account for a greater incidence of cataract in myopia. Weale[2] quoted Fisher's work[12 13] on lens fibre stress to show that the latently accommodated lens of the hypermetrope would be relaxed, whereas in the myopic eye the lens would be stressed by a continually unrelaxed zonule.

The refractive change through life was studied in detail by Slataper, who showed that a hypermetropic change was normal up to the age of 64, after which refraction levelled out and then changed in the direction of myopia. His series of subjects did not exclude those developing cataract. Since cataract becomes very prevalent after the age of 60,[15-18] Slataper's subjects would have included a high proportion of cataract patients in the older age groups. Indeed Slataper himself considered that the myopic change which he recorded in old age was due to cataract, a deduction which is confirmed by the present study. When cases with cataract are excluded, it is seen that a continuing hypermetropic refractive change is found in the healthy eye in old age (Table 3 and Fig. 5). The finding of a myopic refractive change in a seemingly healthy eye in a middle aged or older person should therefore be considered as an indication of impending cataract.

The incidence of the different types of cataract – cortical, nuclear, and subcapsular (Table 1 and Fig. 4) – appears similar to that observed by Foster and Benson[19] in patients presenting with reduced visual acuity due to cataract at a hospital in Leeds. Direct comparisons cannot be made because they classified mixed types of opacities separately and did not relate the incidence to age. In the present study it is noteworthy that subcapsular cataract is the first to appear, presenting in the 40–44 year age group, since it is in the younger age groups that the ophthalmologist is most often asked to determine whether a cataract is spontaneous or due to exposure to drugs, irradiation, or other cause. Thus the identification of a cataract as subcapsular is not in itself evidence of a probable external cause. Perkins [3] recorded a higher incidence of subcapsular cataract at 40% compared with 24% in the present study. The difference can be accounted for by his patients having more advanced cataract than those in the present study. A patient presenting with cortical or nuclear cataract will often develop subcapsular cataract later, which will bring them to hospital because of its more disabling effect on visual acuity. The reported incidence of subcapsular cataract is still lower in other series: 6% in Foster and Benson's series,[19] 10% in Kirby's series,[20] and only 1·8% in Chatterjee's series.[21]

Conclusion

This study shows that simple myopia does not appear to predispose to cataract. It is the development of the cataract itself, in particular nuclear sclerosis, which causes the refractive change towards myopia. The myopic change precedes the development of recognisable cataract, and it can be shown by using Bayesian statistics[22] that the probability of a person over the age of 55 having nuclear sclerosis, given a refractive change of at least −1·00 D over four years, is 0·99. The healthy aging eye continues to show a gradual hypermetropic change.

We are grateful to Dr B C Reeves for computing assistance.

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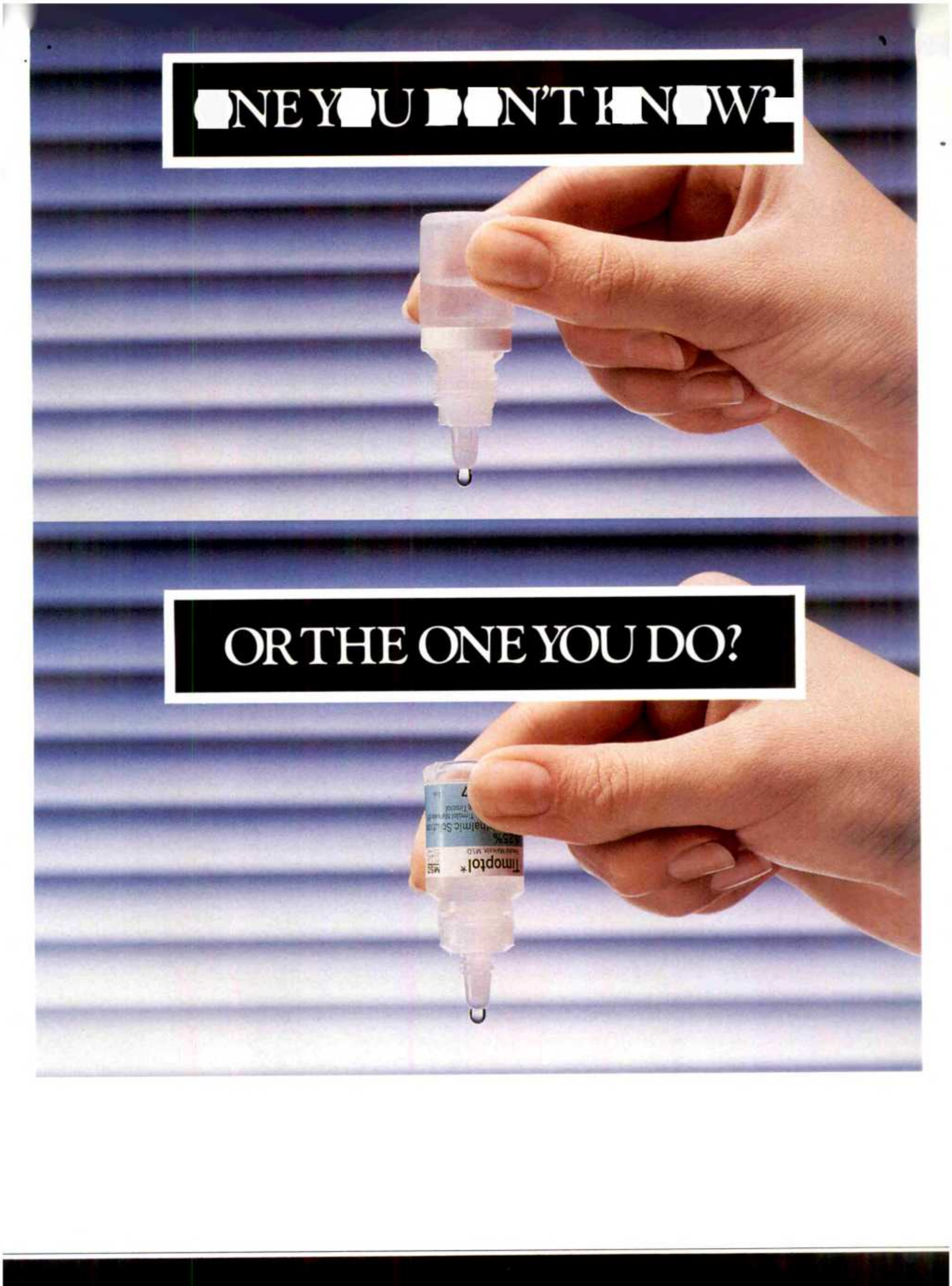

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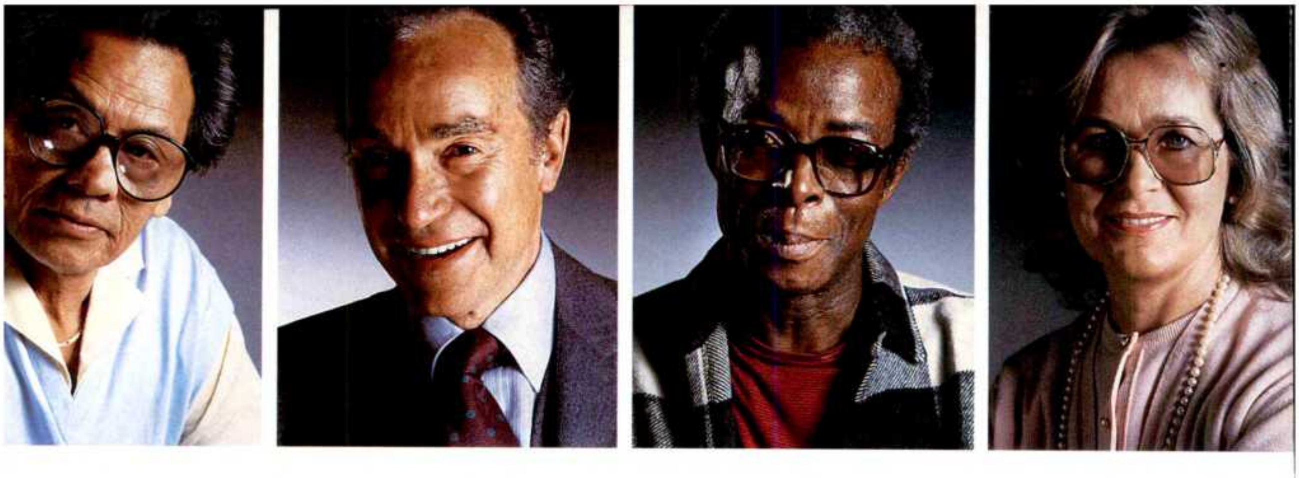

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British Journal of Ophthalmology, 1987, **71**, 415–417

Cyclosporin therapy in Mooren's ulcer

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SUMMARY Mooren's ulcer is a rare disease of presumed autoimmune aetiology. Some cases run a chronic severe course and fail to respond to local and systemic therapy. We report here such a case with bilateral Mooren's ulcer that failed to respond to local therapy with topical corticosteroids, silver nitrate, and conjunctival resection, as well as systemic immunosuppression with corticosteroids, cyclophosphamide, and azathioprine. Systemic cyclosporin (10 mg/kg/day) resulted in resolution of the corneal ulceration within two weeks of beginning treatment, and the patient has remained in remission after 15 months of therapy. Cyclosporin side effects included hirsutism, hypertension, increased blood levels of urea and creatinine, and abnormalities in liver function tests. All these resolved on reducing the dosage of cyclosprin. The results in this case suggest that cyclosporin is an effective agent in patients with severe sight threatening Mooren's ulcer.

Mooren's ulcer is a chronic ulcerative disease of the cornea of unknown aetiology. Patients with this disease have destruction of the peripheral cornea with marginal ulceration, which progresses circumferentially round the limbus. The ulcer has a characteristic overhanging edge and is associated with stromal destruction. Recent evidence indicates that immune mechanisms may be involved in the pathogenesis of this disease, as affected patients have autoantibodies to conjunctival and corneal epithelium.[1 2] Furthermore immunoglobulins (IgG and IgE), complement, and mast cells have been found in the conjunctival epithelium adjacent to ulcers.[3] Other patients have been shown to have abnormalities in cell mediated immunity, including the demonstration of positive migration inhibition factor tests in response to corneal antigens,[4] and abnormalities in peripheral blood T cell subsets.[5] These observations have led to the hypothesis that the abnormalities in this disease may be the result of T cell mediated mechanisms or abnormalities in T cell control. Therefore it seemed logical to suspect that the relatively T cell selective immunosuppressive agent cyclosporin may be effective in the treatment of this disease.

We describe here the successful use of systemic cyclosporin in a patient with severe, previously refractory, bilateral Mooren's ulcer.

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Case history

A 31-year-old Caucasian female presented in the third month of her third pregnancy in December 1982 with bilateral corneal ulceration. Initial treatment consisted of topical corticosteroids. However, her disease remained clinically active until she was referred to one of us (LPR) in March 1984.

Visual acuity was 6/9 in the right eye and 6/60 in the left eye. The right cornea had two large ulcerated areas with undermined edges extending from 6.30 to 8.30 o'clock, about 2 mm from the limbus. The left cornea was severely damaged and had a healed ulcer running through 360° with some active ulceration in the limbal area at 7.30 (Fig. 1). The whole cornea was very thin. There was no significant associated systemic disease. Four weeks after her initial consultation there was perforation of the ulcer in the active ulcerating area of the left eye.

The patient underwent a successful penetrating keratoplasty of the left eye (disparate donor graft size 9·5 mm in 9·0 mm). Four weeks after the operation the graft suddenly became oedematous and there were changes indicative of graft rejection. The patient was treated with topical prednisolone acetate eye drops and subconjunctival betamethasone. At the same time the right eye developed several small superficial infiltrates in the peripheral cornea at 6.30 and 11.00 o'clock. The patient was started on naproxen (250 mg bd) and colchicine (0·5 mg tds),

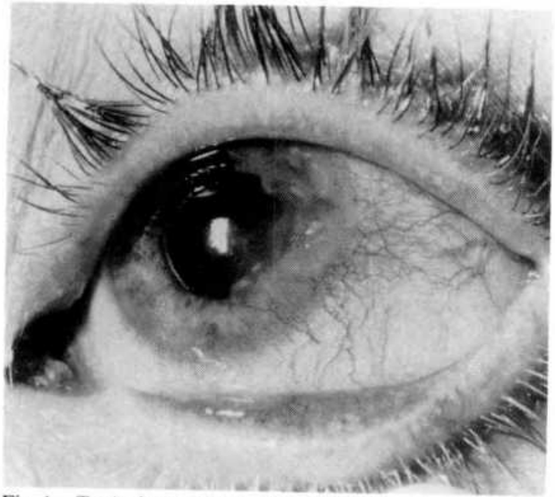

Fig. 1 *Typical area of active Mooren's ulceration involving the temporal cornea of the left eye. Note the undermined central ulcer edge and corneal infiltrate in the leading edge. There are prominent areas of new vessel ingrowth in the ulcer floor. The adjacent peripheral conjunctiva is injected and elevated.*

with little effect on the signs of corneal graft rejection. Subsequently she was given pulsed doses of intravenous methylprednisolone (MP)—1 g intravenously on three occasions during the first week and subsequently 500 mg intravenously at weekly intervals for the next four weeks. The area of corneal ulceration appeared to heal on this pulsed steroid regimen. There was some clearing of the corneal oedema in the left corneal graft.

The patient was subsequently started on oral prednisolone, beginning with 50 mg in the morning and cyclophosphamide 100 mg in the morning (2 mg/kg/day). On this regimen the corneal ulcers in the right eye recurred and required debridement and resection of the adjacent conjunctival area. At the same time the area of active inflammation was treated topically with 1% silver nitrate. The right cornea subsequently healed and the left corneal graft remained clear. The prednisolone therapy was subsequently reduced at a rate of 2·5 mg weekly. The corneal graft in the left eye remained clear, though there was recurrence of ulceration in the right eye.

Three months after the start of cyclophosphamide the disease flared up in the right eye with an area of confluent corneal staining running along the inferior margin from 5.00 to 8.00 o'clock. There were several small oval areas of staining in the normal cornea at 10.00, 3.00, and 4.00 o'clock. The left graft became oedematous, and keratic precipitates were present on the lower third of the cornea. The patient was given an increasing dosage of prednisolone of 100 mg in the morning and started on azathioprine 100 mg (2 mg/kg/day) in the morning. Over the next two weeks there was improvement in the right eye and clearing of the left corneal graft. The patient was nauseated by the medication and developed abnormal liver function as well as marked cushingoid side effects from the steroids. The previously normal results of the liver function tests showed a marked elevation in the alkaline phosphatase (186 U/l; normal range 25–110 U/l), gamma glutaryl transferase (GGT) (239 U/l; normal range 5–50 U/l), aspartate transaminase (76 U/l; normal range 5–35 U/l), and alanine transaminase (65 U/l; normal range 5–35 U/l). At the same time there was recurrence of ulceration in the right eye, and a decision was made at this stage to give the patient cyclosporin 20 ml (10 mg/kg/day) daily.

Two weeks after the start of this therapy there was marked improvement in the right eye, with only mild staining along the ridge separating the normal cornea from the previously ulcerated area. The left cornea cleared. Visual acuity in the right eye was 6/6 and in the left eye was 6/9. Four weeks after the start of the cyclosporin the prednisolone dosage was decreased to 37·5 mg and the cyclosporin dosage decreased to 15 ml daily. The right eye continued to remain clear, with no signs of active ulceration, and the left corneal graft remained clear, with visual acuity of 6/9.

Over the next six months the prednisolone therapy was decreased gradually, and finally withdrawn with no relapse of the disease. Cyclosporin was subsequently decreased, at a rate of 2·5 ml/month. The patient is at present on no systemic medication, with no evidence of disease relapse after 15 months of therapy.

Side effects due to cyclosporin included marked facial and body hirsutism, increased blood pressure (150/100 mmHg), which was controlled with propranolol 20 mg bd, a raised blood urea (10·5 mmol/l) and creatinine (0·13 mmol/l; normal range 0·06–0·11 mmol/l) and abnormal liver function tests as outlined above. The patient tolerated these symptoms well and all side effects have subsequently abated on the reduced dosage of cyclosporin.

RESULTS OF INVESTIGATIONS

On presentation the patient's erythrocyte sedimentation rate was 15 mm/h. The white cell count was $11{\cdot}2\times10^9$/l with 85% neutrophils and 7% lymphocytes. The haemoglobin was 13·6 g/dl. The urea was 4·8 mmol/l and the creatinine was 0·08 mmol/l. Tests for antinuclear antibody and rheumatoid factor were negative. Serum immunoglobulins were within the normal range with an IgA of 1·3 g/l (normal range 0·7–4·5 g/l), IgG of 8·5 g/l (normal range 7–16 g/l), IgM of 2·4 g/l (normal range 0·8–2·5 g/l), and an IgE of 3 IU/l (normal range 0–150 IU/l). The total haemolytic complement (CH50) was 87% (normal range 68–138%), the Clq was 0·15 g/l (normal range 0·15–0·23 g/l), the C4 was 0·43 g/l (normal range 0·17–0·46 g/l), and the C3 was 0·92 g/l (normal range 0·65–1·26 g/l), all within the normal range. The patient was anergic on delayed hypersensitivity skin testing with tuberculin, and mumps, candida, tetanus, streptococcal, and trycophyton antigens. Analysis of the T cell subsets revealed 0·4×10^9/l helper (OKT4) T lymphocytes (normal range 0·7–0·17×10^9/l), 0·2×10^9/l suppressor (OKT8) T lymphocytes (normal range 0·4–1·0×10^9/l), 0·6×10^9/l T (OKT 11) lymphocytes (normal range 1·0–2·3×10^9/l), and the Ia positive cells were 0·14×10^9/l cells (normal range 0·05–0·25×10^9/l). The T4:T8 ratio was 2·3 (normal range 1·2–2·7).

Discussion

Cyclosporin has been shown to be effective in suppressing the underlying autoimmune response in a variety of inflammatory diseases of the eye, especially uveitis, and recently in two complicated cases with a peripheral corneal melting syndrome complicating Wegener's syndrome and scleritis.[6,7] In our patient cyclosporin was introduced after an adequate trial of a variety of other immunosuppressive agents, including systemic corticosteroids, azathioprine, and cyclophosphamide. Each of these immunosuppressive agents has been previously reported to be of value in the management of patients with Mooren's ulcer.[8] However, none of these medications alone or in combination controlled the ocular disease process in this case. Following the introduction of cyclosporin there was resolution of the Mooren's ulcer, and the disease was well controlled for the duration of follow-up.

The mode of action of cyclosporin is not completely understood, but appears in part to be related to the generation of interleukin 2 by helper T cells.[9] The selective ability of cyclosporin to interfere with the action of IL2 makes it an ideal agent for the treatment of diseases that are believed to be mediated by T cells. Rahi[5] has recently reported T cell abnormalities in a patient with Mooren's ulcer, and the results in our case confirm such T cell abnormalities (T cell lymphopenia and anergy) in patients with Mooren's ulcer.

Cyclosporin has a number of well characterised side effects, some of which were observed in our patient.[10] These include the marked hirsuting effect of this drug when used over a long period of time. The patient also had a consistently raised blood urea and creatinine, together with abnormal liver function tests. Elevated blood pressure has also been previously reported as a complication of cyclosporin treatment.[11] Nussenblatt *et al.*[11] have recently reviewed the systemic side effects of cyclosporin in patients with uveitis, and these appear to be less severe than in patients receiving cyclosporin for transplantation and graft rejection related disorders. A number of reasons have been proposed for this observation, including the fact that lower doses of cyclosporin are required to control these diseases than are required in patients undergoing organ transplantation. The most worrying side effect of cyclosporin, namely lymphomas, appears also to be less frequent in patients treated with this drug for diseases not associated with organ transplantation.[12]

This case report illustrates the therapeutic benefit of cyclosporin in a previously refractory case of Mooren's ulcer. Our observation highlights the possible involvement of T cell mediated mechanisms in the pathogenesis of this disease and suggests that a controlled trial should be undertaken of the use of cyclosporin in severe refractory cases of Mooren's ulcer.

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An evaluation of the anti-inflammatory effect of flurbiprofen after cataract extraction

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SUMMARY Thirty-eight patients requiring cataract extraction were randomly assigned to receive either flurbiprofen 100 mg twice daily in addition to routine postoperative therapy or the routine therapy alone. The trial was single blind with clinical assessments at postoperative days 1, 3, 7, 14, and 28. All measures of inflammatory response were significantly less in the group of patients receiving flurbiprofen, and in most cases the clinician's assessment as to which group each patient belonged to was correct. This trial suggests that flurbiprofen reduces inflammatory response in the eye in the first few days following cataract extraction and may therefore reduce the risk of severe and potentially disastrous reactions which sometimes occur.

It is to be expected that after cataract extraction patients will develop some symptoms of ocular inflammation. Traditionally this is treated with local steroid drops, and if it becomes severe systemic steroids may be used.[1 2] There are numerous well documented hazards associated with steroid therapy, but it is imperative that, when an eye does react badly to surgery, the inflammatory process be kept to a minimum, thus reducing the amount of damage to extra and intraocular tissues, particularly the latter. Intraocular tissues involved in any severe inflammatory process quickly lose their vitality, with subsequent loss of functions. This can be irreversible with permanent visual loss.

Flurbiprofen is a propionic acid derivative with potent analgesic, antipyretic, and anti-inflammatory properties.[3 4] It is rapidly absorbed after oral administration, giving peak serum concentrations within approximately one and a half hours. The drug does not accumulate to any marked extent on repeat dosing. Many clinical trials have established the efficacy of flurbiprofen in rheumatic and associated conditions, and its safety has been established in controlled long-term studies.[5 6] Wide clinical usage has confirmed these findings over several years.[7-10]

This trial reports the effect of giving flurbiprofen for the reduction of postoperative ocular inflammation.

Material and methods

The protocol required that 40 patients of any age and either sex who needed cataract extraction, and had given informed, written consent, be admitted to the study. The cataracts were removed intracapsularly without intraocular lens implantation by a microsurgical technique using cryoextraction and by a standardised technique for all patients. All patients were given 1% chloramphenicol ointment immediately the surgery was completed, and then 0·5% chloramphenicol drops four times daily for 10 days postoperatively. Aqueous samples were removed from 10 patients (Table 1).

Table 1 *Preoperative levels of flurbiprofen in aqueous humour following an oral dose of 100 mg three hours previously*

Patient Number Receiving tablets orally	*Concentration flurbiprofen NG/ML aqueous humour*
T1	18
T2	9
T3	13
T4	14·5
T5	22
T6	20
T7-T10	Volume submitted insufficient (less than 20 µl)

Number of patients: 6. Mean concentration 16·1 ng flurbiprofen per ml aqueous humour (SD 4·8).
SI conversion: ng/ml = µg/l.

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The patients were admitted on a random basis to one of two groups, one of which received no additional routine therapy and the other flurbiprofen 100 mg twice daily by mouth. The first dose of flurbiprofen was given three hours prior to the operation, and subsequent doses with breakfast and the evening meal for a period of 10 days. This study was single blind, so that if an eye deteriorated suddenly the clinician could immediately ascertain to which group the patient belonged and act accordingly. In normal circumstances, however, the clinician was not aware of which patients were receiving flurbiprofen. Patients with a known hypersensitivity to non-steroidal anti-inflammatory drugs (NSAIDs), or patients currently being treated with one of these preparations, were excluded.

Past medical and ocular history were recorded as well as the results of a detailed preoperative ocular examination. The trial began on the day of operation (day 0), and the results of clinical examinations were recorded on days 1, 3, 7, 14, and 28. These examinations included the condition of the lids, conjunctiva, cornea, and anterior chamber plus any other observations the clinician considered worth recording. Each parameter was graded I to IV by the guidelines given in Table 2.

Operative details and any complications were recorded on the evaluation sheet, as were severity of any side effects. At the end of the trial the investigating clinician recorded a summary of the patient's progress and also a blind assessment of whether each patient received flurbiprofen or not.

Table 2 *Guidelines for assessing inflammatory response in various ocular tissues*

	Lids	*Conjunctiva*	*Cornea*	*Anterior chamber*
Grade I	Normal	Normal	Normal	Normal
Grade II	Slightly red	Slightly red	Slight haze	Slight flare
Grade III	Red	Red	Infiltrated by cells	Flare
Grade IV	Very red and swollen	Very Red	Cells and corneal folds	Flare and cells

Results

The trial involved 38 cataract extractions, with patients being randomly assigned flurbiprofen 100 mg twice daily or to the control group where no NSAID was taken. One patient in each group had simultaneous bilateral operations, and the recorded results for only one eye have been included for each of these patients. Of the 38 patients who completed the investigation 20 were in the flurbiprofen group and 18 in the control group. The trial was single blind with the clinician not knowing to which group a patient belonged. The patients' ages ranged from 42 to 86 years and a two-sample *t* test showed no significant difference between the groups. The flurbiprofen group consisted of six males and 14 females, and the control group seven males and 11 females. A χ^2 test showed no significant differences between the groups.

The responses for the patients for each individual parameter were tested for significance by a χ^2 test. These results are given in Tables 3 to 6. The results indicate that the eyelids of patients taking flurbiprofen became less inflamed and swollen than in the control group. This tendency was shown after three days, and the difference is statistically significant at the first week. As would be expected, this difference disappeared by days 14 and 28.

The condition of the eyelids was graded I to IV according to the amount of redness and swelling present. The results for the two groups at the various assessment times are given in Table 3. The postoperative state of the conjunctiva was assessed clinically and graded I to IV according to redness present and thus the degree of inflammation. Table 4 gives the results for both groups of patients at each assessment day. The patients taking flurbiprofen showed less redness than the control group, and this is statistically significant at day 3, though the latter group settled with time and the significance disappeared at later assessments.

The postoperative changes in the cornea were evaluated clinically at each assessment day and graded I to IV according to the degree of haze and

Table 3 *Postoperative condition of eyelids*

Postoperative day:	*1*		*3*		*7*		*14*		*28*	
Response	*Flurb*	*Cont*	*Flurb*	*Cont*	*Flurb*	*Cont*	*Flurb*	*Cont*	*Flurb*	*Cont*
I	10	7	13	6	16	6	15	12	17	15
II	9	11	7	8	2	11	3	5	0	1
III (and IV)	1	0	0	4	1	0	0	0	0	0
Total	20	18	20	18	19	17	18	17	17	16
p value	NS		NS		<0·01		NS		NS	

Flurb = flurbiprofen. Cont = control.

Table 4 *Postoperative conjunctival changes*

Postoperative day:	*1*		*3*		*7*		*14*		*28*	
Response	*Flurb*	*Cont*	*Flurb*	*Cont*	*Flurb*	*Cont*	*Flurb*	*Cont*	*Flurb*	*Cont*
I	0	1	0	2	4	2	10	3	15	10
II	18	15	19	8	12	13	7	13	2	6
III	2	2	1	8	3	2	1	1	0	0
Total	20	18	20	18	19	17	18	17	17	16
p value	NS		<0·01		NS		NS		NS	

Table 5 *Postoperative condition of the corneas*

Postoperative day:	*1*		*3*		*7*		*14*		*28*	
Response	*Flurb*	*Cont*	*Flurb*	*Cont*	*Flurb*	*Cont*	*Flurb*	*Cont*	*Flurb*	*Cont*
I	6	4	13	5	16	5	15	10	17	14
II	13	10	5	6	1	9	2	7	0	2
III	1	4	2	7	2	3	1	0	0	0
Total	20	18	20	18	19	17	18	17	17	16
p value	NS		<0·05		<0·01		NS		NS	

Table 6 *Clinical condition of the anterior chambers*

Postoperative day:	*1*		*3*		*7*		*14*		*28*	
Response	*Flurb*	*Cont*	*Flurb*	*Cont*	*Flurb*	*Cont*	*Flurb*	*Cont*	*Flurb*	*Cont*
I	6	3	13	4	16	5	14	11	17	15
II	11	10	5	5	1	5	3	6	0	1
III	3	5	2	4	2	7	1	0	0	0
IV	0	0	0	5	0	0	0	0	0	0
Total	20	18	20	18	19	17	18	17	17	16
p value	NS		<0·05		<0·01		NS		NS	

cells present. These findings are recorded in Table 5. The patients taking flurbiprofen showed significantly less corneal reaction at day 3 ($p<0{\cdot}05$) and day 7 ($p<0{\cdot}01$) than the control group. As time progressed to days 14 and 28 the inflammatory reaction of the control group also settled, and as expected the significance levels again disappeared.

The postoperative condition of the anterior chamber was also assessed and, using the degree of flare and the presence of cells, graded I to IV. The results at each assessment day are given in Table 6. These results show that patients taking flurbiprofen had less reaction in the anterior chamber than the control group and that this difference was statistically significant at day 3 ($p<0{\cdot}05$) and day 7 ($p<0{\cdot}01$). No patient in the flurbiprofen group was reported to have cells in the anterior chamber as compared with five reports in the control group.

These results indicate that in every parameter assessed there were significant advantages to the patients in the flurbiprofen group as compared with the controls. These advantages were most marked in

Table 7 *Clinician's assessment of whether patient taking flurbiprofen*

Clinician's opinion	*Flurbiprofen group*	*Control group*
On flurbiprofen	17	4
Not on flurbiprofen	2	13
Unsure	1	1
Total	20	18

Table 8 *Reasons for patients failing to complete the trial*

Patient	*Age*	*Sex*	*Day of last assessment*	*Flurbiprofen*	*Reason for withdrawal*
9	76	F	7	Yes	Visual hallucinations and confusion
15	75	F	3	Yes	Abdominal pains and vomiting
38	78	F	14	Yes	Late flare—topical steroids
2	66	M	3	No	Allergic response to chloramphenicol
24	85	F	14	No	Bad flare up

the first few postoperative days, as one would expect. This period is when the patient is most at risk from inflammation.

The clinician made an overall assessment on a blind basis to decide whether each individual patient had received flurbiprofen or not, and these results are given in Table 7. There was a strong relationship between the clinician's opinion and whether or not the patient was taking flurbiprofen; this is statistically significant ($p<0{\cdot}01$). In the majority of cases it was clinically apparent that patients given flurbiprofen showed less inflammatory response than the control group.

Five patients failed to complete the study and these details are given in Table 8.

NSAIDs are known to cause gastric irritation in susceptible patients, and probably patient 15 had drug complications. There were no other withdrawals which seem likely to be drug related, nor were there any adverse effects reported in patients taking flurbiprofen. It should be noted that patient 38 was withdrawn on day 14 because of a late flare up which occurred four days after cessation of flurbiprofen. It is possible that continuing flurbiprofen for a few more days would have avoided this occurrence.

Discussion

In this single-blind study of the anti-inflammatory effect of flurbiprofen following cataract extraction it was clearly demonstrated that patients receiving the drug had much quieter eyes than those without NSAID. The development of ocular inflammation is usual after cataract extraction and can sometimes be very serious. The use of a potent anti-inflammatory agent such as flurbiprofen appears to reduce this risk without an unacceptable risk to the patient from side effects.

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A study of the value of the central and peripheral isoptres in assessing visual field progression in the presence of paracentral scotoma measurements

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SUMMARY The visual field records of 45 eyes of 45 patients were evaluated to determine whether examination of the peripheral field of vision in patients with glaucoma and field defects adds useful information about the progression of visual field damage. The central scotoma mass, foveal sensitivity, and the central and peripheral mass of the visual field were quantified from measurements on the Tübinger perimeter. Most of the information on visual field progression was contained in the scotoma mass. When both scotoma mass and foveal sensitivity were known, central or peripheral isoptres did not add statistically significant information on progression. Evaluation of scotomas and assessment of central isoptres or of foveal sensitivity made perimetry of the peripheral isoptres redundant. The appearance of fresh peripheral scotomas or the quantification of changes in peripheral scotomas was not examined in the current study, and they would of course be important when they occurred.

The examination of the field of vision is important when monitoring patients with glaucoma. Decisions on the adequacy of therapy are often based on whether visual field damage is progressing. The evaluation of the field of vision will always involve some compromise, because the patient's cooperation in visual field testing and the time for perimetry are not unlimited. It is not practicable to examine every possible retinal location in detail. Strategies which will maximise the diagnostic information in a minimum of time have to be developed.

We have previously shown that progressive visual field damage results in an increasing density of existing paracentral scotomas, their enlargement, or the development of new paracentral scotomas in previously unaffected areas of the visual field.[1] Of those patients showing progressive visual field damage 24% showed an increase in density of the scotomas as the only manifestation of change, 7% developed scotomas of larger area, and 14% developed new scotomas as their only sign of progression. This suggests that, when perimetry is performed in glaucoma patients, threshold information of disturbed points in a scotoma as well as careful delineation of the area of scotomas and examination of the unaffected areas of the visual field are necessary, because any of these can take place as an isolated sign of progression. The rate of progression of field loss varies between patients. However, most patients whose defects deteriorate show either a linear or a curvilinear mode of visual field progression.[2] It is not clear whether examination of the peripheral isoptres in patients with glaucoma and field defects adds useful information about the progression of visual field damage, when careful perimetry of the central isoptre and the quantitative perimetry of all scotomas in the central field are available. Detailed examination of the peripheral isoptres involves further time which could be saved if it is not informative. A retrospective study to try partly to evaluate this question was therefore performed.

Material and methods

The charts of glaucoma patients for whom demographic data were stored on computerised records

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were reviewed. These computerised records were chosen because of the easy access to data such as visual acuity, intraocular pressure, drugs, and details of any surgery. Only patients with routine chronic open-angle glaucoma and pressures greater than 21 mmHg were selected. Patients with low tension glaucoma were excluded. All patients were part of one of our practices (SMD) and were followed up routinely. Very few, if any, were followed up because of any particular difficulties with their management. To qualify for the study the patients had to have paracentral or arcuate defects within the central 30° and 22 months or more of follow-up after the development of the field defects. Forty five eyes of 45 patients (26 males and 19 females) were reviewed. Their ages ranged from 35 to 84 years (mean 61·0 (SD 9·5) years; median age 61·7 years). The follow-up periods ranged from 22 to 182 months (mean 91·2 months (SD 46·3), median 96·0 months.)

The fields were recorded both kinetically and statically on the Tübinger perimeter, whose records are large enough for planimetry. All perimetry was performed according to a standard protocol followed in our laboratory. Without a corrective lens the peripheral isoptres were initially plotted with a 10-minute target size and at least the 1000 and 100 apostilb intensities. A lens was then inserted into the lens holder and static threshold testing was performed to obtain superior profiles at 45° and 135° and inferior profiles at 225° and 315°. These profiles were obtained with 1° stimulus separation. Central kinetic perimetry was then performed with a range of stimulus intensities of 3·2, 6·3, 10, 16, 32, 100, and 1000 apostilbs, all with a 10-minute target size. As many stimulus intensities were used as was necessary to quantify completely the size and depth of any existing scotomas and to give a maximum rendering of the isoptres centrally. Static screening was then performed on 75 points at the 2½°, 5°, 10°, and 15° circular positions. This was to cover any areas unchecked by static profiles.

All patients had to have an initial visual acuity of 20/30 or better and a final visual acuity of 20/40 or better. The planimetry of the visual field records was carried out on the Zeiss video plan to determine the area of the scotomas within the central 30°. The areas within the central and peripheral isoptres were also examined by planimetry, and the foveal sensitivity was recorded.

Each scotoma was delineated by plotting its size to many stimuli. For a sequence of successively increasing stimuli, scotoma areas (mm^2) specific to a given stimulus were multiplied by the logarithm of the corresponding stimulus intensity as measured in apostilbs. For example, suppose that the outer rim of a scotoma was outlined by a stimulus of log intensity I_1, (Fig. 1), enclosing a total area of A_1 mm^2, and that the next stronger stimulus, of log intensity I_2, ($I_2 > I_1$), delineated an inner, deeper scotoma within the first, with an enclosed area of A_2 mm^2 ($A_2 < A_1$). Then the total 'mass' of this scotoma consisted of two components: an outer ring of area $A_1 - A_2$ mm^2 and of 'depth' I_1, and within it an additional core of area A_2 mm^2 and of 'depth' I_2. The masses corresponding to these two components were then summed to yield, for this scotoma, an estimated total mass of

$$(A_1 - A_2)I_1 + A_2I_2 = A_1I_1 + A_2I_2 - A_2I_1$$

in mm^2×decibel units. The sum of all total scotoma masses in the inner 30° was used to represent the total visual loss for a given field.[2] Only true scotomas completely surrounded by areas of greater sensitivity were measured. If a scotoma broke through to the periphery it continued to contribute to the total scotoma mass at the level at which it was observed just prior to breakthrough. The position of the isoptres was not used to determine the scotoma mass, and therefore nasal steps or generalised or localised depressions did not enter into the calculation of scotoma mass but would of course influence the measurements made from the relevant isoptres.

All the area measurements used were those plotted on the visual field records of the Tübinger perimeter. These visual field records are flat representations of the spherical retinal surface and are therefore subject to systematic distortions. There is no distortion at the point of fixation which corresponds to the fovea. However, it increases progressively towards the periphery of the visual field in that there is an overestimation of area of loss in the periphery as compared with the corresponding retinal area. Although we were using planimetric measurements

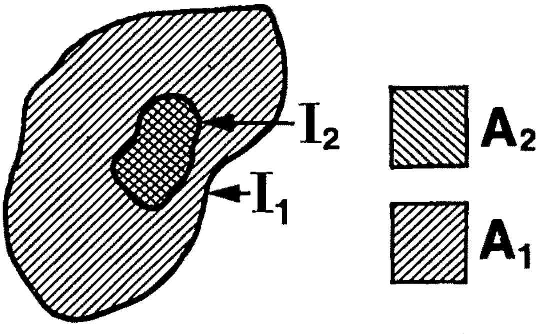

Fig. 1 *A schematic representation of a scotoma and the calculation of its mass. A stimulus of log intensity I_1 has delineated the scotoma shown, enclosing a planimetrically determined total area of A_1 mm^2. A stronger stimulus, of log intensity I_2, has outlined within the first scotoma a deeper region of area A_2 mm^2. The total scotoma mass was therefore estimated as*

$$(A_1 - A_2)I_1 + A_2I_2 \text{ mm}^2 \times \text{decibels}$$

recorded from both the central and peripheral isoptres, which were therefore subject to these distortions, we disregarded the distortion, since our calculations were not meant to measure the absolute amounts of visual field loss but to evaluate the change of the visual field and the usefulness of information obtained from these records for the follow-up of glaucoma patients. Furthermore, since projection distortions are constant from eye to eye, they were unlikely to affect the intrasubject correlation studies. The visual field records used in Oculus perimetry are equidistant azimuthal polar projections. This projection is equidistant on the meridians only. Areas enclosed by a closed line on the sphere are not directly proportional to the corresponding area on the surface of the projection. With an equivalent azimuthal polar projection the area enclosed by a closed curve on the sphere is directly proportional to the corresponding area on the plane chart.[3] To obtain a rough approximation of the amount of error introduced into our planimetry calculations with the Oculus perimeter we performed a comparison between the areas enclosed within the central 10° as compared with the areas enclosed between the 10 and 20 and 20 and 30°. The error obtained was less than 3%.

QUANTIFICATION METHODS

Five field related parameters in each eye were defined with regard to glaucomatous progression over time.

The foveal sensitivity ('sen') was obtained directly from the static profiles at each field test, and expressed in decibel units (decimal logarithm of apostilbs).

The scotoma mass (SM) in mm²×decibel units was calculated from each visual field examination according to the method already fully described.[2]

The central mass (CM) of the island of vision, peripheral mass (PM), and total mass (TM) were defined and quantified. They were determined from each set of perimetric charts, measuring respectively the central (inner 30°), peripheral (beyond 30°), and total mass of the remaining 'island' of vision. Since the intensity to plot the largest isoptre used was 1000 apostilbs, 'sea level' for the island was set at $\log_{10} 1000=3$. This level was recalibrated as 'height 0' (Fig. 2). The height of the central top of the island was then set to correspond to the logarithm to base 10 of the sensitivity at fixation (0°). Successive concentric isoptre areas corresponding to increasing stimulus intensities were measured planimetrically in mm² from the 30° perimetric chart. This information was expressed geometrically, leading to the progressive construction of the central 30° portion of the island of vision. The top component of island mass was approximated by a cone, its base positioned at a height corresponding to the decimal logarithm of the stimulus intensity of the most central isoptre, and having a circular area corresponding to the planimetrically established area within that isoptre. Its vertex was the point corresponding to the logarithm of sensitivity at fixation. The cone volume (mass) (M_1 in Fig. 2) was then geometrically calculated.

For the purpose of calculating the island, the radius r of the base of this cone had to be measured in degrees from fixation. This was done by calculating planimetrically the total 30° circular area of the standard 30° perimetric chart (=25 544 mm²), and then solving the proportionate formula,

$$\frac{r^2}{30^2}=\frac{A_1}{25\,544}$$

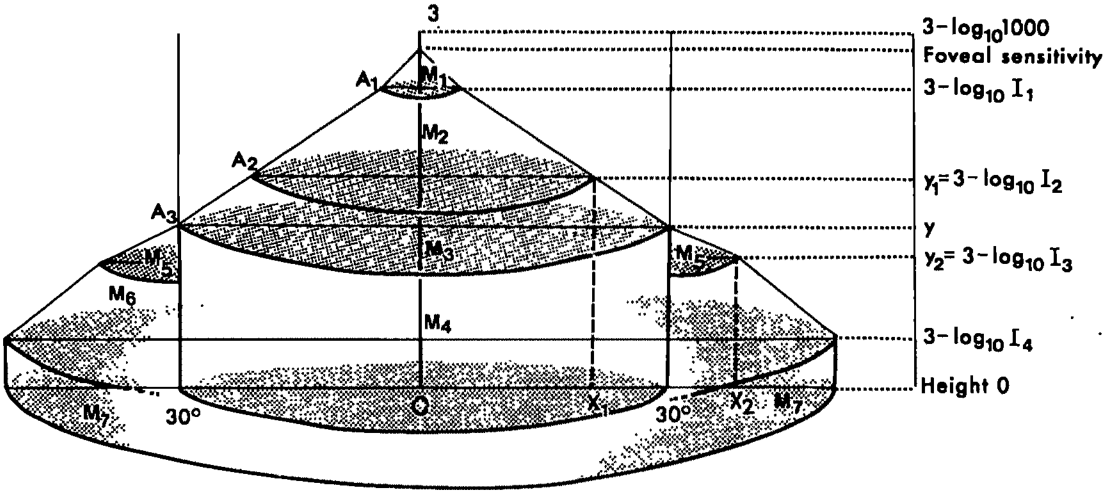

Fig. 2 *The quantification of mass of the visual field.*

where A_1 was the central isoptre area. This was followed by successively increasing isoptre areas to stronger stimuli producing a descending sequence of slices in the shape of truncated cones. The masses of these slices (M_2 in Fig. 1) were calculated geometrically.

The largest central isoptre available was generally well within the 30° central perimetric circle. To estimate the logarithm of the sensitivity as it would be at 30° the largest central and the smallest peripheral isoptre heights were used. A scale adjustment had to be introduced, since on the peripheral perimetric chart, constructed on a larger scale, the area of the central 30° circle of the field was only 2 783 mm². Thus the radius x_1 of the largest central isoptre was again expressed in degrees from fixation by solving the formula

$$\frac{x_1^2}{30^2}=\frac{A_k}{25\,544}$$

where A_k was the area of the largest (k'th) central isoptre. Analogously, the radius x_2 of the smallest peripheral isoptre, in commensurate units of degrees from fixation, was calculated from

$$\frac{x_2^2}{30^2}=\frac{A_{k+1}}{2\,783}$$

where A_{k+1} was the area of the smallest peripheral isoptre determined from the peripheral chart.

If y_1 represented the height corresponding to x_1, and y_2 corresponding to x_2, the sensitivity level y at 30° was then calculated by simple linear interpolation between y_1 and y_2. This provided another truncated cone, below which was a cylindrical slice filling out the foundation of the central island out to 30° (Fig. 2). The component masses obtained from the top cone, the truncated cones, and the bottom cylinder were added to yield an estimated central mass, in mm²× decibel units.

A similar technique with some modifications was used to calculate the peripheral mass of the island from which the central mass was removed. The periphery terminated with a centrally hollow truncated cone resting at sea level whenever the largest stimulus used was 1000 apostilbs; otherwise a centrally hollow cylinder formed the foundation of the peripheral island, with a height related to the logarithm of the largest stimulus intensity plotted.

To obtain total island mass the central and peripheral masses were first made comparable by means of a factor which adjusted for the scale difference between the central and the peripheral perimetric charts; they were then added to each other.

It may be noted that the calculation of the total mass of the island was based on the assumption that successive cross-sectional isoptre areas were circular in shape. Although the observed shapes were not always strictly circular, a classical theorem in solid geometry, known as the Cavalieri principle,[4] guarantees that the circularity assumption yields the correct mass.

STATISTICAL METHODS

The data to be analysed consisted of 45 eyes of 45 patients, in each of whom a sequence of observations over time was available from which the foveal sensitivity (decimal logarithm), scotoma mass, central mass, peripheral mass, and total mass could be calculated. In addition the initial age and other demographic variables were available.

To examine the progression of any of these variables over time, linear regression on time within patients was carried out, and a weighted time slope was calculated and tested for significance by standard analysis of covariance techniques.[5] Similar methods were used for correlating any two out of the five variables. Such methods were generally warranted by the reasonably symmetrical, light-tailed distributions of the residuals examined.[6] To compare how much of the information about progression was contained in each of the five variables, adjustments were first carried out within patients, whereby a set of the variables (or a single variable) were first 'partialled out' by multiple (or simple) regression followed by the calculation of the adjusted residuals. These were then regressed against time within patients, following the same method of analysis of covariance.

Results

It was clear that progression was demonstrated by SM increasing significantly with time (Table 1). It could also be noted that sen, CM, PM, and TM significantly decreased with time (Tables 2–5).

SM, as expected, was highly negatively correlated with all four of the other field variables (Tables 1, 2). It was further noted that, when adjusted for sen, SM still progressed over time with high statistical significance (Table 1). Similarly, adjusting SM for any of the field mass variables (CM, PM, or TM) reduced the time correlation only slightly (from 0·96 to 0·76).

It should also be noted that only the sen time slopes were correlated with age ($p=0\cdot032$; $r=-0\cdot31$). The mean sen level observed for each patient also correlated highly with age ($p=0\cdot0019$; $r=-0\cdot44$). None of the other variables was age related. No significant differences in the progression rates for any of the field variables discussed could be found to correspond to the linear or quadratic modes of progression of scotoma masses previously described.[2] A highly significant positive correlation could be found between all pairs sen, CM, PM, and TM (Tables 2–5).

Table 1* *Scotoma mass (central field) in progression*

Dependent variable	*Adjusted for*	*Independent variable*	*Slope†*	*Correlation†*	*Coefficient of determination*	*p‡*
SM	—	t	24·469	0·963	0·927	0
	sen	t	19·652	0·728	0·530	0
	CM	t	18·065	0·764	0·584	0
	PM	t	18·223	0·758	0·574	0
	TM	t	17·374	0·759	0·576	0
	—	CM	−0·0859	−0·930	0·865	0
	—	PM	−0·278	−0·932	0·869	0
	—	TM	−0·0259	−0·933	0·870	0
	CM	PM	−0·0460	−0·481	0·231	NS
	PM	CM	0·0119	0·597	0·356	NS

*Adjusted for patient effects.
†Partial slope (correlation) whenever variable has been adjusted in column 2.
‡0=0·00000; NS: not significant (p>0·05).
SM=scotoma mass (mm^2×decibels); t=time (months); sen=foveal sensitivity ($\log_{10}$); CM=central mass (mm^2×decibels); PM=peripheral mass (mm^2×decibels); TM=total mass (mm^2×decibels).

Table 2* *Foveal sensitivity in progression*

Dependent variable	*Independent variable*	*Slope*	*Correlation*	*Coefficient of determination*	*p†*
sen	t	−0·0172	−0·823	0·677	0
	SM	−0·00025	−0·698	0·487	0·0001
	CM	0·00016	0·852	0·726	0
	PM	0·00038	0·827	0·684	0
	TM	0·00039	0·836	0·699	0

*Adjusted for patient effects.
†0=0·00000.
Abbreviations as in Table 1.

Table 3* *Central field mass in progression*

Dependent variable	*Adjusted for*	*Independent variable*	*Slope†*	*Correlation†*	*Coefficient of determination*	*p‡*
CM	—	t	−68·110	−0·833	0·694	0
	sen	t	−34·943	−0·450	0·202	0
	SM	t	−15·965	−0·306	0·094	0·016
	sen, SM	t	−8·805	−0·229	0·052	NS
	SM, PM	t	2·816	0·199	0·040	NS
	—	PM	1·965	0·925	0·856	0
	SM	PM	1·337	0·699	0·489	0

*Adjusted for patient effects.
†Partial slope (correlation) whenever variable has been adjusted in column 2.
‡0=0·00000; NS=not significant (p>0·05).
Abbreviations as in Table 1.

Table 4* *Peripheral field mass in progression*

Dependent variable	*Adjusted for*	*Independent variable*	*Slope†*	*Correlation†*	*Coefficient of determination*	*p‡*
PM	—	t	−20·897	−0·782	0·612	0
	sen	t	−13·712	−0·446	0·199	0
	SM	t	−4·685	−0·343	0·118	0·04
	sen, SM	t	−3·742	−0·274	0·075	NS
	SM, CM	t	−1·726	−0·277	0·077	NS
	SM	CM	0·144	0·730	0·533	0

*Adjusted for patient effects.
†Partial slope (correlation) whenever variable has been adjusted in column 2.
‡0=0·00000; NS=not significant (p>0·05).
Abbreviations as in Table 1.

Table 5* *Total field mass in progression*

Dependent variable	*Adjusted for*	*Independent variable*	*Slope†*	*Correlation†*	*Coefficient of determination*	*p‡*
TM	—	t	−259·91	−0·814	0·662	0
	scn	t	−160·80	−0·462	0·213	0
	SM	t	−58·96	−0·342	0·117	0·02
	scn, SM	t	−43·16	−0·265	0·070	NS

*Adjusted for patient effects.
†Partial slope (correlation) whenever variable has been adjusted in column 2.
‡0=0·00000; NS=not significant (p>0·05).
Abbreviations as in Table 1.

Discussion

In spite of the fact that patients were selected into this study who maintained a fairly constant visual acuity throughout the follow-up period, a marked, highly statistically significant progression can be observed over time in all visual field parameters (but not all patients). It is apparent, however, that among the parameters considered the paracentral scotoma mass contains most of the information about progression and is hardly affected by the additional knowledge of the central or peripheral isoptres. On the other hand the information bearing on progression contained in any of the other visual field mass measurements considered here is only slightly significant when the paracentral scotoma mass is known and adjusted for, and becomes non-significant when both the scotoma mass and foveal sensitivity are recorded.

It is also interesting to note that the peripheral mass sheds no further light concerning progression when the paracentral scotoma mass and the central mass are known. It should also be noted that the central mass gives no further information with respect to progression when both the paracentral scotoma mass and the peripheral mass of the visual field are known. This, however, would not be the case in standard perimetry, which concentrates almost exclusively on the inner 30° of the field.

While the paracentral scotoma mass carries the major information regarding the progression of the visual field in glaucoma, any one of the other measures—foveal sensitivity, central mass, or peripheral mass—carries some additional information about progression of field loss. It is therefore likely that they are all manifestations of a diffuse change which affects them all.

It would appear that in perimetry of glaucomatous progression the accurate quantitation of paracentral scotomas and the assessment of the central isoptres or foveal sensitivity make perimetry of the peripheral isoptres redundant. It must be stressed that the present study did not consider the appearance of fresh peripheral scotomas, which would be important when they occurred. The examination of the peripheral field for the occurrence of fresh scotomas or change in existing scotomas in the peripheral field should still not be abandoned until specific investigation of the peripheral scotomas has been undertaken.

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Posterior synechiae after glaucoma operations: aggravation by shallow anterior chamber and pilocarpine

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SUMMARY Posterior pupillary synechiae affect a proportion of eyes subjected to iridectomy with or without drainage operation because (1) aqueous humour bypasses the pupil; (2) traumatic iridocyclitis occurs; (3) there is immobility of the iris in the iridectomy sector; (4) in eyes with angle closure glaucoma closer apposition of the iris to the anterior lens capsule increases the tendency; (5) pilocarpine aggravates (4) both in angle closure glaucoma and open angle glaucoma and produces a small immobile pupil facilitating pupillary membrane formation (occlusio pupillae). Pilocarpine should be avoided if possible as medical treatment at any time after a drainage operation. A beta blocker is the drug of choice. To eliminate posterior synechiae over a fair number of degrees of pupil (say 30°) sector iridectomy can be done.

Iridectomy is a well established procedure in the treatment of glaucoma,[1] specifically angle-closure glaucoma (ACG).[2] In patients with closed-angle glaucoma (CAG) 45–70% of untreated fellow eyes will develop closed angles within 10 years of initial presentation.[3 4] Prophylactic peripheral iridectomy—or laser iridotomy—is therefore advocated for prevention.[5] There are some complications of surgical iridectomy.[5-8] However, these are usually considered to be infrequent or innocuous enough, so that the operation is done in preference to the risk of acute closed-angle glaucoma.

This paper examines the prevalence and distribution of posterior synechiae, a common side effect of surgical procedures in the treatment of glaucoma—particularly of surgical iridectomy—and the role of postoperative pilocarpine as an aggravating factor, especially in eyes with shallow anterior chambers.

This series preceded our adoption of laser iridectomy for ACG, but, as far as posterior synechiae are concerned, laser iridectomised eyes behave very much like eyes which have had surgical iridectomy.[9 10] Indeed, posterior synechiae are easier to miss after laser iridectomy, so that the surgeon must remain vigilant with this newer treatment.

Patients and methods

Retrospective analysis of 63 consecutive patients attending a glaucoma clinic who were operated on for glaucoma determined the prevalance of postoperative posterior synechiae and their association with the postoperative administration of pilocarpine. Sixty-three eyes from 63 patients (mean age 69·8, SD 10·4 years) were included in the study. There were 39 eyes from 39 patients with closed-angle glaucoma (mean age 69·0, SD 9·9 years) and 24 eyes from 24 patients with open-angle glaucoma (mean age 71·0, SD 11·1 years). There was no significant sex predilection (30 males : 33 females). Patients with 'secondary' glaucoma were excluded. All patients had had glaucoma operations during the preceding 15 years. The classification of surgical procedures is shown in Table 1. A detailed history was recorded from each patient, with particular reference to postoperative medical treatment, which information was available from the case records. The presence of posterior synechiae was assessed by (attempted) dilatation of pupils by guttae 1% tropicamide and guttae 10% phenylephrine. A diagram of the ensuing pupil size and shape was drawn, and the presence or absence of posterior synechiae noted on a clock diagram divided into 12 sectors.

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Only one eye was chosen from each patient, since both eyes in one patient can be expected to behave similarly; thus each individual observation would not then be completely independent of all others. The choice was random: right eyes were chosen from patients whose years of birth ended in even numbers and left eyes from odd numbers.

Results

Comparisons were made between the prevalence of posterior synechiae in patients who had required operation for ACG/CAG (excluding acute cases) and for open-angle glaucoma (OAG). Each group was subdivided into those who had or had not required pilocarpine afterwards. Assessments were 'single masked,' and significance was assessed by the χ^2 test with Yates's correction. The results are shown in Tables 2 and 3.

Even without pilocarpine some posterior synechiae were present: 6/19 for CAG (Table 2) and 2/10 for OAG (Table 3). Although the proportion is higher for CAG, the difference is not significant ($\chi^2=0{\cdot}05$, DF=1, $p>0{\cdot}05$).

The presence of posterior synechiae was highly significantly associated with postoperative pilocarpine as judged by a comparison between eyes which had received no pilocarpine at any time after operation and those which had received the miotic, in each category separately: see Table 2 for closed-angle glaucoma ($\chi^2=14{\cdot}4$, DF=1, $p<0{\cdot}001$), and Table 3 for open-angle glaucoma ($\chi^2=10{\cdot}3$, DF=1, $p<0{\cdot}001$), and both together CAG+OAG ($\chi^2=27{\cdot}1$, DF=1, $p<0{\cdot}001$). The type of iridectomy performed was not a significant factor in the predisposition to posterior synechiae in closed-angle glaucoma patients, there being no significant difference between the prevalence of posterior synechiae in patients who had sector iridectomy and those who had peripheral iridectomy ($p>0{\cdot}05$).

Fig. 1 shows a typical eye with ring posterior synechiae, only revealed by powerful mydriatics.

The sectors of pupillary circumference occupied by posterior synechiae are shown in Table 4 (and diagrammatically in Fig. 2). 83% of all patients had either no posterior synechiae (40%) or total posterior synechiae (43%); only 17% had an intermediate degree of posterior synechiae (95% confidence interval: 9%–25%). Of those eyes developing posterior synechiae there was involvement of the whole pupil circumference in 76% of CAG patients, which is more than the 62% found in open-angle glaucoma patients (71% of all glaucoma subjects), but this difference was not significant ($\chi^2=0{\cdot}31$,

Table 1 *Glaucoma surgery in 63 eyes from 63 glaucoma patients*

	Closed-angle glaucoma	*Open-angle glaucoma*
Peripheral iridectomy	22	3
Trabeculectomy	5	11
Sector iridectomy	5	0
Sector iris inclusion	2	2
Scheie's operation	3	2
Trephine	2	6
Total	39	24

Table 2 *Prevalence of postoperative posterior synechiae in 39 eyes from 39 patients with closed-angle glaucoma*

	Posterior synechiae absent	*Posterior synechiae present*
No pilocarpine postoperatively	13	6
Pilocarpine postoperatively	1	19

$\chi^2=14{\cdot}4$, DF=1, $p<0{\cdot}001$.

Table 3 *Prevalence of postoperative posterior synechiae in 24 eyes from 24 patients with open-angle glaucoma*

	Posterior synechiae absent	*Posterior synechiae present*
No pilocarpine postoperatively	8	2
Pilocarpine postoperatively	1	13

$\chi^2=10{\cdot}3$, DF=1, $p<0{\cdot}001$.

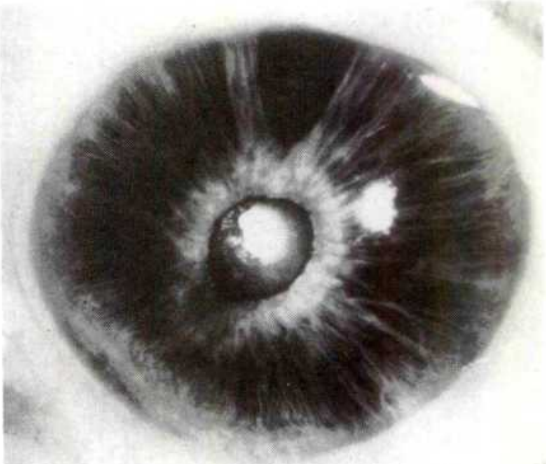

Fig. 1 *Total posterior synechiae in an eye operated on for chronic CAG—owing to the bypassing of the pupil by aqueous, plus traumatic iridocyclitis, aggravated by pilocarpine and a shallow anterior chamber—become obvious only when strong mydriatics are used.*

Table 4 *Proportion of pupil circumference occupied by posterior synechiae in 63 eyes from 63 glaucoma patients*

	0°	30°	60°	90°	120°	150°	180°	210°	240°	270°	300°	330°	360°
Closed-angle glaucoma (n=39)	14	2	2	1	0	0	1	0	0	0	0	0	19
Open-angle glaucoma (n=24)	11	1	2	0	0	0	2	0	0	0	0	0	8
Total (n=63)	25	3	4	1	0	0	3	0	0	0	0	0	27

DF=1, p=>0·05). Of eyes with subtotal posterior synechiae the peripheral iridectomy quadrant was always involved (other sectors might be free from posterior synechiae), but the numbers were too small for analysis.

Discussion

The prevalence of posterior synechiae in closed-angle glaucoma following peripheral iridectomy, without postoperative pilocarpine, has previously been reported to be 33% with a predilection for the iridectomy quadrant.[11] In the present study the prevalence of posterior synechiae in closed-angle glaucoma following a number of different surgical procedures in patients not treated with postoperative pilocarpine was remarkably similar at 32%. In ACG patients after peripheral iridectomy alone the prevalence was 3/12 or 25%. A similar tendency exists in cases of laser iridectomy, with a prevalence reported as 14%[9,10] Almost all the points discussed here can be applied to this newer technique. Three of 22 patients developed posterior synechiae after argon laser iridectomy, prevented in 19/22 by topical steroids and mydriasis.[9] In patients with open-angle glaucoma the prevalence of posterior synechiae in patients not treated with postoperative pilocarpine was 2/10 or 20% (Table 3).

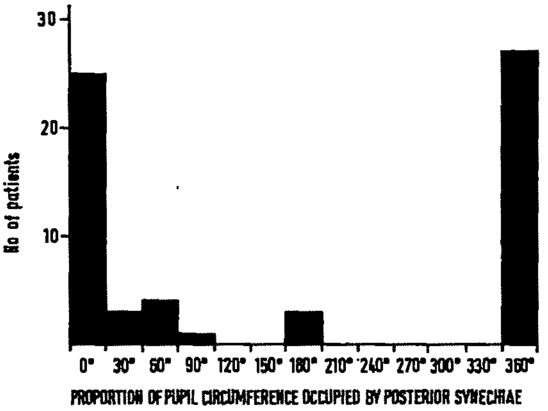

Fig. 2 *Proportion of pupil circumference occupied by posterior synechiae.*

A clinician may remain complacent about the prevalence of posterior synechiae in his surgical cases unless and until he has reason to attempt to dilate the pupils with a mydriatic.

Given the validity of the proposition that posterior synechiae do not develop spontaneously in a normal eye (we present no evidence here, other than clinical impression, for that null hypothesis), it is noteworthy, though not surprising, that 8/29 eyes (Tables 1 and 2) not receiving postoperative pilocarpine developed posterior synechiae, in spite of mydriatic treatment, with or without steroids, in the immediate postoperative period. We would attribute that finding to several factors in order of importance:

(1) All aqueous humour will take the line of least resistance through the iridectomy (peripheral or sector), so that no aqueous flow will lift the pupil as it enters the anterior chamber.

(2) In the immediate postoperative period some generalised traumatic iridocyclitis must be present to make the whole iris sticky and synechiae-prone.

(3) In eyes with peripheral iridectomy the remaining bridge of iris between pupil and iridectomy probably suffers ischaemic inflammation as well as a greater traumatic iridocyclitis than other areas of iris (that property would be minimal in laser iridectomy).

(4) In eyes with peripheral iridectomy, especially large ones, the involved sector of iris will be relatively immobile, hence tending to allow posterior synechiae to form more readily because of factors 1 to 3 above (a minimal effect in laser iridectomy).

As the prevalence of posterior synechiae in ACG and OAG patients treated with postoperative pilocarpine was 95% and 93% respectively, one may reasonably conclude there was a significant association with miotics.

From first principles, and because of the slightly higher prevalence of posterior synechiae in ACG patients (32%) than in OAG patients (20%), we would add to the above list:

(5) In ACG patients greater pressure contact between iris and lens because of the more anterior plane of the pupil in ACG eyes than in OAG eyes.

Since pilocarpine almost eliminated that 32% versus 20% discrepancy, two further aggravating factors are added:

6 (*a*) Immobility of the pupil miosed by pilocar-

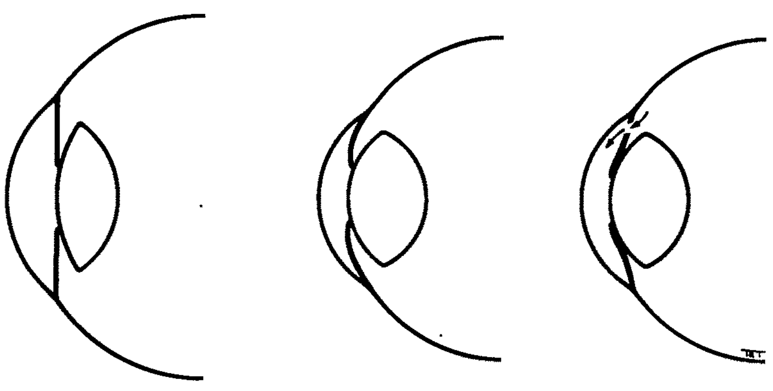

Fig. 3 *The emmetropic or myopic eye on the left has less risk of posterior synechiae because the pupil probably exerts little pressure on the lens. The iris on the right is very likely to develop wide posterior synechiae, especially if inflamed by operative traumatic iridocyclitis and/or miotic treatment, because aqueous humour will take the line of least resistance through the peripheral iridectomy, leaving a wide area of iris constantly pressing on the anterior lens surface. The central diagram shows an eye predisposed to angle-closure glaucoma, with iris bombé.*

pine; (*b*) even greater pressure contact between iris and lens in both ACG and OAG eyes because of pilocarpine than implied in (5) above.

Anatomical predisposing factors in the pathogenesis of posterior synechiae are illustrated in Fig. 3.

A further disastrous consequence of the small miosed pupil is the ease with which a membrane may fill it (occlusio pupillae), resulting in loss of vision. We have not tried optical iridectomy alone in such cases, because they are impossible to differentiate clinically from cataract.

We also suspect that the posterior synechiae in iridectomised ACG eyes will be more extensive radially than in OAG eyes, but evidence for that would be difficult to obtain.

It is our clinical impression that, once posterior synechiae have started, it is difficult to prevent their spreading to involve the whole pupil, since immobility of the pupil immediately adjacent to an established synechia must facilitate the advance. Even frequent movement of the free areas of pupil by maximal atropine or other anticholinergic plus sympathomimetic will mitigate that fixity only to a limited extent. Table 4 and Fig. 2 (as well as Fig. 1) we would interpret as strongly supporting that 'all-or-none' phenomenon. 40% of eyes show no posterior synechiae, and 43% show total posterior synechiae, whereas only 17% show an intermediate involvement (with a 95% confidence interval of 9%–25%).

Seclusio pupillae (100% posterior pupillary synechiae) can readily occur in eyes which have had iridectomy, because no aqueous will pass under and lift the pupil, preferring the line of least resistance through the iridectomy. The presence of the iridectomy allows the eye to avoid iris bombé of course.

DELETERIOUS EFFECT OF POSTERIOR SYNECHIAE

Do posterior synechiae matter? We have already mentioned above the tendency for a membrane to form across the miosed pupil. We would also expect posterior synechiae to become predisposed in the course of time to cataract formation because of damage to the lens capsule. By analogy there is some support for that from the generally accepted view that a penetrating injury or iridocyclitis tends to be complicated by cataract, at least in the long term. We will not present some statistics which did show a lower visual acuity in eyes with total posterior synechiae (i.e., peripheral iridectomy) than in others (most with sector iridectomy), because the surgeons were different in the two groups.

In all five eyes which suffered flat chamber for several days immediately after drainage operations (these eyes have not been included in the series reported here), the visual acuity was eventually reduced to counting fingers or hand movements. It would not be justifiable to blame the total posterior synechiae entirely for the very poor vision due to eventual cataract.

Apart from the risk of occlusio pupillae and cataract, fixity of the pupil in response to light and the near reflex will probably be little handicap.

PREVENTION

Even if the possible deleterious effects mentioned in the preceding paragraph are denied, it would nevertheless be reasonable to claim that, if posterior synechiae can be prevented by safe treatment, that should be done. Steroids or non-steroidal anti-inflammatory drugs for several weeks before and after operation probably have a place, in spite of the added risk of infection when the former are used. In the immediate postoperative period we aim to keep the pupil semidilated *and* moving, with careful monitoring especially to avoid overdilatation in ACG. For a blue iris or easily dilated pupil (for example, in a younger person) tropicamide 1% each evening supplemented by adrenaline 1:1000 or phenylephrine 5% each morning (lest systemic absorption of the adrenergic at night produce insomnia) for 7–10 days will usually suffice. In dark brown or very immobile irises homatropine or even atropine each evening or twice daily, plus phenylephrine 10% each morning, may be necessary.

A closely similar situation arises with posterior synechiae in iridocyclitis, although aqueous *is* passing through the pupil in these eyes. In cases of iridocyclitis we apply maximum effort to avoid *any* posterior synechiae, or to eliminate them entirely if at all possible, by means of subconjunctival glucocorticoid and mydricaine plus maximum mydriatics (atropine *and* phenylephrine) at the patient's first visit. Repeat maximal mydriasis often succeeds in breaking down residual synechiae on the 2nd or 3rd day following subconjunctival steroids, unless of course the iridocyclitis is long-standing. If some residual posterior synechiae remain, we prescribe atropine and phenylephrine 10% (the latter several times daily), at least while there is active iridocyclitis and for some weeks afterwards to impose maximum movement on sectors of free pupil, which minimises the spread from foci of fixed posterior synechiae.

We avoid pilocarpine if at all possible when medical treatment is required to control pressure at any time postoperatively, even long after the operation, because of the very high risk of total posterior synechiae.

In this situation we regard a topical beta blocker as the first line of defence, and it is usually adequate, because it has no effect on the pupil. Timolol's effectiveness after operation on CAG is already established.[12] (We also regard a beta blocker as a valuable adjuvant to weak pilocarpine for a fellow ACG eye awaiting iridectomy, because the reduced production and flow of aqueous humour will reduce the height of the iris bombé. The same consideration will apply to those occasional patients who unfortunately refuse both surgical and laser iridectomy.) Occasionally pilocarpine does have to be added to a beta blocker, but we are always very reluctant to do that.

A PLACE FOR SECTOR IRIDECTOMY

If we suspect that an eye will need medical treatment, especially pilocarpine, after operation for glaucoma, we perform a sector iridectomy. Indeed, the need for medical supplementation to a drainage operation is frequent enough, especially in the long term, for us to favour sector iridectomy in most drainage procedures. Rather similarly, in ACG eyes which we judge may not respond completely to peripheral iridectomy, surgical or laser, but which probably do not need a drainage procedure, we do a sector iridectomy. In the latter case our rationale is twofold: in the operation of sector iridectomy the iris has to be pulled well out of the eye to allow the pupil to present, so that the breaking down of the freshest goniosynechiae inferiorly is facilitated, unlike the situation in the less disturbing peripheral iridectomy.[12–16] A more important rationale applies to both groups, whether or not pilocarpine is used after operation: even if a membrane does spread inwards into the pupil area from the edge of a pupil immobilised by total posterior synechiae, in the sector where the pupil margin is missing that complication cannot occur. The British climate makes the glare through a sector iridectomy more tolerable than in sunnier situations.

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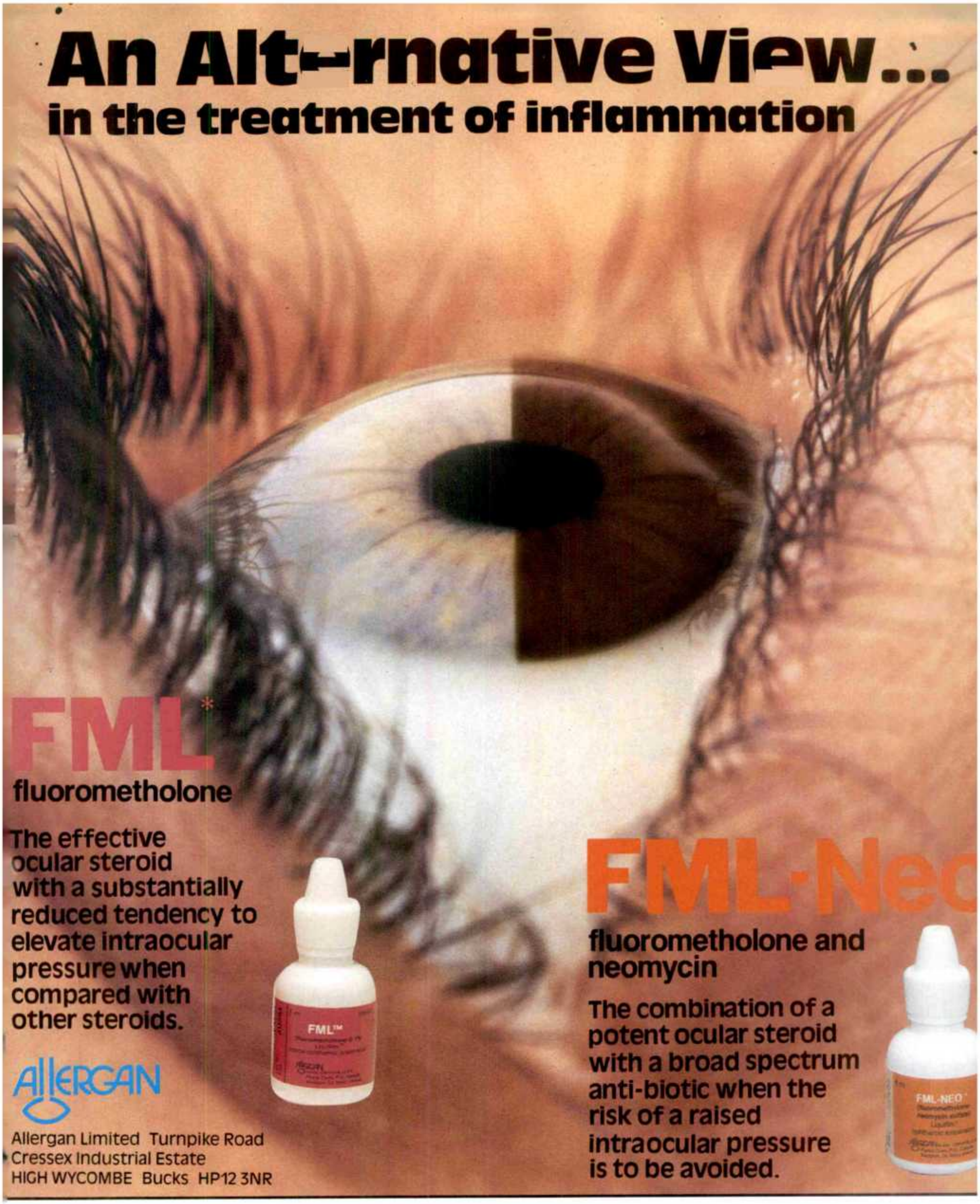

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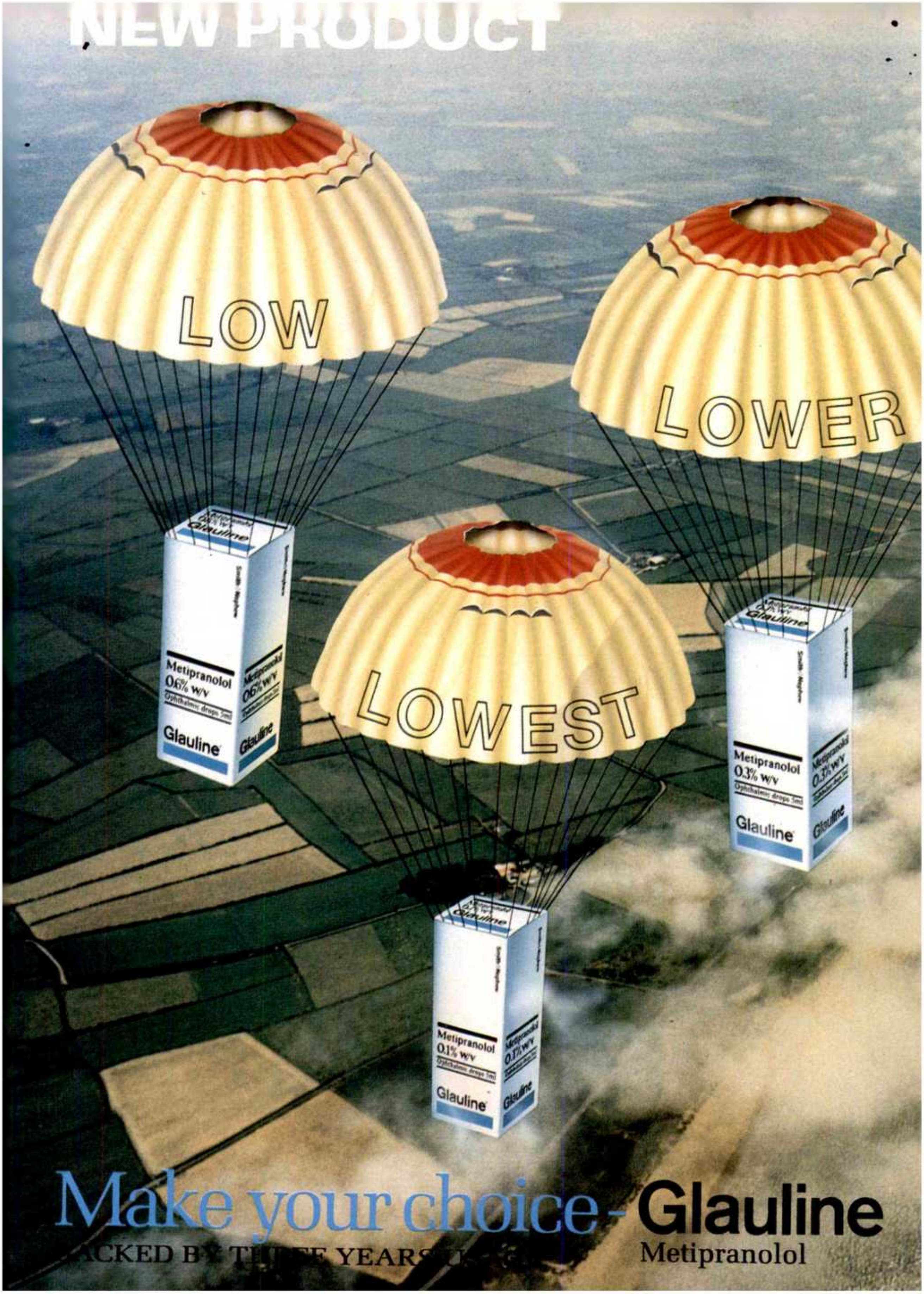
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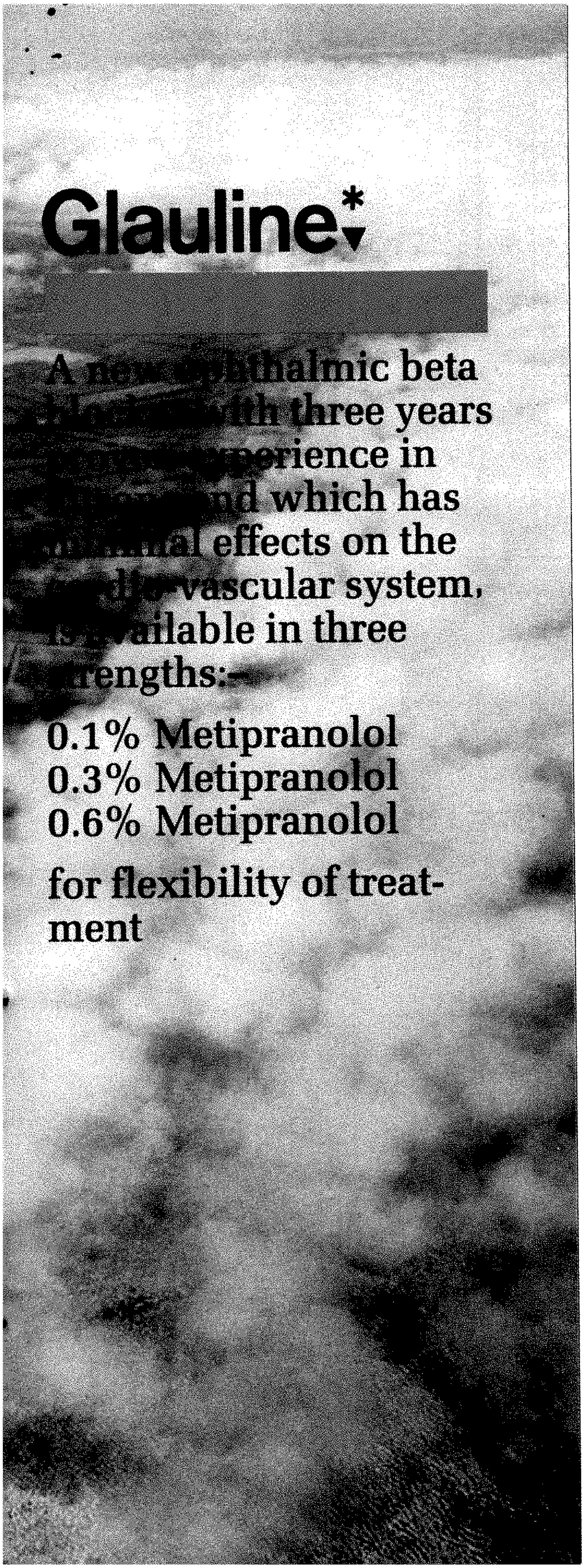
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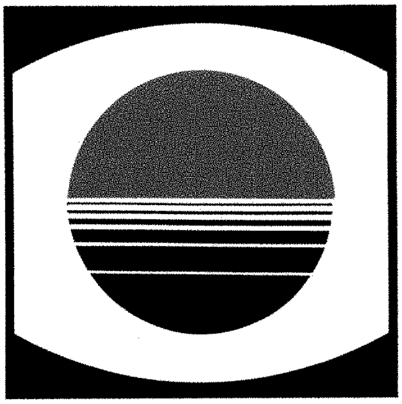

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D B CLEMENTS[1] AND V TAILOR[2]

From [1]Whiston Hospital, Prescot, and [2]Glaxo Laboratories Ltd

SUMMARY Patients undergoing cataract surgery may develop an infective endophthalmitis postoperatively which may result in the loss of an eye. This study was carried out to measure aqueous humour levels and to assess patients' tolerance of ceftazidime, a potent antipseudomonal cephalosporin, given subconjunctivally. Eighteen patients received 125 mg ceftazidime subconjunctivally before they underwent routine cataract surgery. A further two patients received 62·5 mg subconjunctivally. The results show good penetration into the aqueous humour well above the minimum inhibitory concentrations (MICs) of possible pathogens. There were no postoperative infections, no local irritation, and no systemic side effects.

Ceftazidime (Fortum) is a third generation, parenteral cephalosporin, which is active against a wide range of Gram-positive and Gram-negative organisms, including pseudomonas.[1-3] It is a bactericidal antibiotic, which is stable in the presence of β-lactamases.

Previous studies have shown that after intravenous administration adequate levels are achieved in the human eye to eradicate the majority of organisms found in ophthalmic infections.[4-6] However, improved penetration could be achieved at the site of infection by administering the drug subconjunctivally. Studies measuring the ocular penetration of ceftazidime in humans following subconjunctival injections have not so far been published.

Materials and methods

Before the start of the study approval from the hospital's ethical committee was obtained. Patients who had given their informed consent received a preoperative subconjunctival injection of ceftazidime at varying time intervals before undergoing routine cataract surgery. Patients with a past history of hypersensitivity to penicillins or the cephalosporins were excluded from the trial. Preoperative investigations of all patients included serum creatinine and haemoglobin levels.

The ceftazidime solution was reconstituted by mixing 250 mg of ceftazidime powder with 1 ml of sterile water for injection. The freshly prepared solution had a volume of 1·2 ml. The 18 patients who received 125 mg of ceftazidime were given 0·6 ml of the solution, while the two patients who received a dose of 62·5 mg ceftazidime were given 0·3 ml of solution subconjunctivally. The operations were carried out under local or general anaesthesia.

In the course of the operation 10 ml of blood was first withdrawn from the cubital vein. At the same time the aqueous humour was aspirated with a fine 27 gauge needle attached to a 1 ml insulin syringe. Penetration of the eye was at the limbus in the temporal position. The aqueous humour sample was placed in a small bottle. At this stage a section was made at the limbus with a diamond knife in order to remove the cataract.

Storage of all samples was at −70°C. Blood samples were first clotted and only the serum was stored. Sample assays were carried out by high performance liquid chromatography.

Results

Ceftazidime levels obtained in the aqueous humour and serum of all the patients entered in the trial are shown in Table 1. One patient (patient G) had a ceftazidime level of 1·08 μg/ml in the aqueous humour 14½ hours after his subconjunctival dose. The remaining patients underwent surgery 37 minutes to 4 hours after receiving the ceftazidime dose. The aqueous humour levels ranged from 17·3

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Table 1 *Aqueous and serum levels following subconjunctival injections of 125 mg ceftazidime*

Patients	*Post injection Sample time (hr and min)*	*Ceftazidime concentration (µg/ml)*	
		Aqueous humour	*Serum*
A	0·37	77·12	1·47
B	1·14	194·57	6·20
C	2·08	97·06	5·90
D	0·14	153·60	3·30
E	0·16	164·00	3·80
F	1·05	38·60	3·00
G	14·30	1·08	0·16
H	1·45	310·40	4·60
I	3·12	198·54	4·21
J	2·24	87·80	4·10
K	1·05	17·30	8·00
L	2·00	200·30	2·30
M	3·22	35·50	4·70
N	2·16	57·40	4·90
O	4·00	85·00	3·10
P	3·10	157·90	3·30
Q	1·20	120·60	3·80
R	2·08	45·20	2·10
Injections of 62·5 mg ceftazidime			
S	3·27	15·56	1·27
T	1·31	24·14	1·56

Patients G, S, and T are not shown in Fig. 1.

to 310·4 µg/ml. These levels are all well above the MICs required for organisms generally isolated after routine cataract surgery (see Discussion).

As expected, the serum levels were much lower than the aqueous humour levels, ranging from 1·47 to 8·00 µg/ml. Nevertheless, these serum levels were still above the MICs for most Gram-negative bacteria.

The aqueous humour levels of ceftazidime are illustrated in Fig. 1, which shows that high levels persisted in the aqueous humour for several hours after the initial subconjunctival injection. It also shows a wide variation in the aqueous humour levels measured in the samples collected (see Discussion).

Discussion

Several investigators have measured the penetration of ceftazidime in the aqueous humour following parenteral administration.[4-6] Walstad and Blika[4] found ceftazidime levels ranging from 11·0 (SD 3·9) to 5·5 (SD 2·7) µg/ml at 1/2 and 5 hours respectively in the aqueous humour following a 2 g intravenous dose.

Axelrod *et al.*[5] measured mean aqueous humour concentrations of 2·80, 4·00, 3·20, 3·39, and 1·94 µg/ml after 1/2, 1, 2, 4, and 6 hours respectively, following a 2 g intravenous dose. Giamarellou *et al.*[6] gave three 1 g doses of ceftazidime by intramuscular injections, and found aqueous humour levels of 1·3 µg/ml and 3·2 µg/ml 2 and 6 hours respectively after the last dose.

The results of the present study show that considerably higher aqueous humour levels are achieved when ceftazidime is administered subconjunctivally (see Table 1). As can be seen in Fig. 1, there is a wide variation in the aqueous humour levels of ceftazidime. This is probably related to the fact that the pharmacokinetics of drugs following subconjunctival injection are very complex.[7] After subconjunctival injection of ceftazidime two routes of intraocular penetration are possible[8]: (1) leakage from the bleb through the needle track into the tear film; (2) direct penetration.

After penetration through the sclera the drug may enter the eye by a number of routes: (1) sideways into

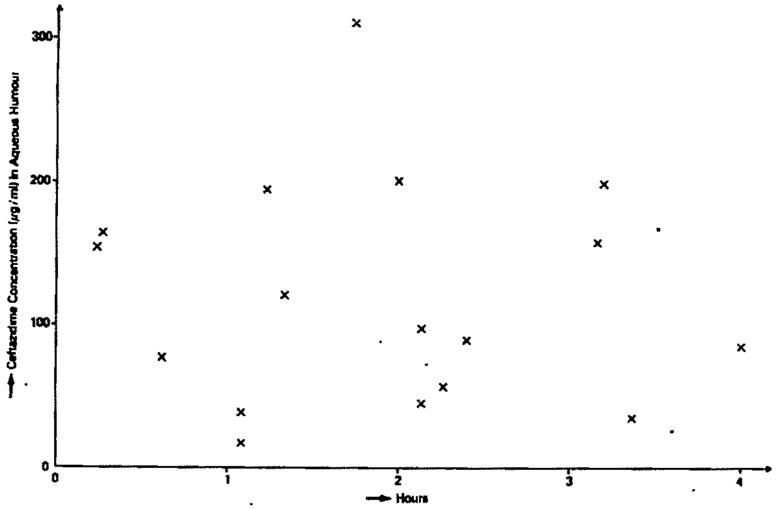

Fig. 1 *Ceftazidime concentration in aqueous humour (µg/ml) versus time after injection (hours) of 125 mg subconjunctival ceftazidime. Patients G, S, and T are omitted.*

the cornea and across the corneal endothelium; (2) across the trabecular meshwork; (3) through the iris and across its anterior surface; (4) into the ciliary body and thus into the aqueous humour. The exact level of ceftazidime at any one time depends on the inflow by the above routes and also the outflow, principally through the canal of Schlemm and determined by the coefficient of outflow value.

The pathogens most commonly causing endophthalmitis are *Staphylococcus aureus, Staph. epidermidis, Pseudomonas aeruginosa, Proteus mirabilis,* indolepositive *Proteus* species, *Escherichia coli, Klebsiella* species, and *Haemophilus influenzae*. Ceftazidime is active against all these organisms. However, higher levels of antibiotic in the eye than those generally achieved by intravenous or intramuscular administration are required to eradicate certain ocular pathogens such as *Staph. aureus* and *Staph. epidermidis*.[9]

After subconjunctival administration the concentration of ceftazidime achieved in the aqueous humour exceeds the MICs of not only pseudomonas, which is generally difficult to treat, but also most *Staph. aureus* and *Staph. epidermidis*. Nevertheless, in sight threatening infections of proved staphylococcal origin it may be more prudent to give an antistaphylococcal penicillin together with the subconjunctival ceftazidime.

The current choice of drugs in the prophylaxis and treatment of endophthalmitis includes an aminoglycoside. The subconjunctival use of gentamicin, either alone or in combination with another antibiotic, is common.[10] Other aminoglycosides used subconjunctivally are framycetin[11] and tobramycin.[10] However, all aminoglycosides have varying degrees of ototoxicity and nephrotoxicity. Although a single subconjunctival dose of an aminoglycoside is unlikely to cause any significant toxicity, this difference could be important in the prolonged treatment of established serious ocular infections.[10] Ceftazidime has a spectrum of activity similar to the aminoglycosides, but it has been shown to be free of the adverse reactions described above for aminoglycosides. Furthermore, many aminoglycoside resistant strains are sensitive to ceftazidime,[12] and Davidson[13] has stated that up to 30% of pseudomonas strains may be resistant to gentamicin.

One factor to be considered is the degree of local irritation resulting from a single subconjunctival injection. In this study subconjunctival ceftazidime did not cause any local irritation, nor were there any systemic side effects. Furthermore, none of the patients developed any postoperative infections.

In conclusion, this study shows that subconjunctival ceftazidime achieves high concentrations in the aqueous humour, indicating that the drug has a place in the prophylaxis and treatment of ophthalmic infections by the subconjunctival route.

Our thanks are due to Glaxo Group Research for the estimation of aqueous and serum levels of ceftazidime.

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The seat belt law and after

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SUMMARY We report a retrospective study of 378 perforating eye injuries presenting between August 1981 and July 1984 to four major teaching hospitals. The aetiological groups have been analysed together and by region, and preventive measures for some groups are discussed. We have confirmed the effectiveness of seat belt legislation in reducing serious eye injury.

It is important to monitor the aetiology of serious eye injuries. Only then will a pattern emerge which may allow recognition of preventable eye disease. Proper action may then be taken to reduce the incidence of such injuries.

This multicentre study reviewed the aetiology of perforating eye injuries 18 months before and after the introduction of seat belt legislation. There were two objectives; firstly, to see whether the reduction in injury from road traffic accidents (RTAs) shown in Hampshire[1] was similar in other regions of the UK, and secondly to assess the present aetiological pattern of perforating injury so that future preventive measures can be considered.

Materials and methods

Four ophthalmological units participated in the study: Manchester Royal Eye Hospital, St Paul's Eye Hospital, Liverpool, the Eye Department of the Royal Hallamshire Hospital, Sheffield, and the Birmingham and Midland Eye Hospital. These centres were chosen because each was the major referral centre for their respective region. Each served industrial and urban communities, and could be expected to receive both motorway and urban RTA referrals.

The theatre registers were used to identify all cases of penetrating eye injury between 1 August 1981 and 31 July 1984. The corresponding medical records were examined. The following parameters were recorded: date of injury, age, sex, detailed aetiological history, details of injury.

The cases were divided into two 18-month periods by their date of injury. Period A was from 1 August 1981 to 31 January 1983, while period B was from 1 February 1983 to 31 July 1984. These represented two equal intervals before and after seat belt legislation.

Each period was then broken down by region and into one of seven aetiological groups as follows: RTA, assault, sporting, occupational, domestic, childhood play, unknown. In the RTA group we recorded both the position of the patient in the vehicle and whether or not a seat belt was worn (if the information was available). An occupational injury was one which occurred at work and as a direct consequence of work. Thus a hammer and chisel injury occurring at home was not included in this group. An injury occurring below the age of 14 (and not an RTA) was classified as childhood play regardless of cause.

Results

The records of 381 perforating eye injuries were reviewed. This figure represented an 83% retrieval. Three of these cases were excluded from analysis because of insufficient recorded information. The results are outlined in Tables 1 to 9.

The overall aetiological pattern of injuries by region is summarised in Table 1. The only significant differences between periods A and B were found in the RTA group. The incidence of RTAs as a cause of perforating eye injury fell from 17·1% (39) to 6% (9) after seat belt legislation. Assaults accounted for 11·1% of all perforating injuries. A regional variation was noted (Manchester 13·4%, Liverpool 13·1%, Sheffield 11·7%, and Birmingham 7·7%), though this trend is not statistically significant (χ^2 test with Yates's correction).

A regional variation was also demonstrated in the

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Table 1 *Aetiology by region and time period*

	Period A					*Period B*					*Total*	*%*
	M	*L*	*S*	*B*	*ST*	*M*	*L*	*S*	*B*	*ST*		
RTAs	11	9	2	17	39	1	1	1	6	9	48	12·7
Assault	8	5	6	4	23	9	3	1	6	19	42	11·1
Sport	4	1	1	5	11	1	1	1	5	8	19	5·0
Domestic	25	4	7	9	45	17	3	6	7	33	78	20·6
Childhood	17	9	5	19	50	12	4	4	11	31	81	21·4
Occupational	11	13	12	22	58	10	8	14	17	49	107	28·3
Unknown	1	0	0	1	2	1	0	0	0	1	3	0·8

ST=subtotal. M=Manchester. L=Liverpool. S=Sheffield. B=Birmingham.

Table 2 *Age ratios*

	Age groups								*M/F*
	0–9	*10–19*	*20–29*	*30–39*	*40–49*	*50–59*	*60–69*	*>70*	
RTAs	2	8	25	6	3	2	1	1	39:9
Assault	—	13	13	2	4	6	2	2	39:3
Sport	—	5	8	5	1	0	0	0	19:0
Domestic	—	18	20	13	9	5	7	6	67:11
Childhood	49	32	—	—	—	—	—	—	63:11
Occupational	—	18	29	26	24	8	1	1	105:2
Totals	51	94	95	52	41	21	11	10	332:36
Percentage	13·4	24·8	25·1	13·8	10·8	5·5	2·9	2·6	

M/F=ratio of male to females. —=Incompatible, see text.

occupational group, which accounted for 28·3% of perforating eye injuries (Manchester 16·5%, Liverpool 34·4%, Sheffield 43·3%, and Birmingham 30%). The differences in the figures between Manchester and each of the other centres are statistically significant by the χ^2 test with Yates's correction (Manchester and Sheffield $p<0{\cdot}01$, Manchester and Liverpool $p<0{\cdot}025$, Manchester and Birmingham $p<0{\cdot}05$).

Table 3 *Position of injured person in car*

Driver	14
Front seat passenger	26
Back seat passenger	3
Unspecified	5

Table 4 *Seat belt status*

	Period A	*Period B*	*Total*
Wearing	2	3	5
Not wearing	27	4	31
No history obtained	10	1	11
Wearing but not fastened	0	1	1

Table 5 *Assault cases—detailed aetiology*

Broken glass	18	Gun	2
Broken bottle	3	Carpet pin	1
Knife	4	Chain	1
Fist	4	Pen	1
Thumbs	3	Karate kick	1
Stone	2	Unknown	4
Pub brawl	2		

In Table 2 the aetiological groups have been broken down by age and sex. As expected the majority of injuries occurred between the ages of 14 and 40. There was an overall male preponderance of 7·8:1, which was particularly striking in the sport, occupational, and assault groups.

Table 3 shows the position of the patient in the car. There were more injuries involving the front seat passenger than the driver (26 against 14). There were only three back seat passenger injuries. Table 4 shows the seat belt status. This was recorded in 37 out of the 48 cases. Thirty one of those 37 cases were not wearing a seat belt. One patient was wearing the seat belt without its being fastened.

Table 5 itemises the weapons used in the assault cases: 50% were caused by a broken glass or bottle.

Table 6 is an analysis of the sporting injuries and shows the frequent association with spectacle breakage (seven out of 17).

The causes of occupational and domestic injuries are given in Tables 7 and 8. There were 30 recorded injuries occurring when a hammer and chisel were being used (23 out of 107 occupational and 7 out of 78 domestic).

Childhood injuries are broken down by cause in Table 9. Of the 81 injuries 11 were caused by a dart.

Table 6 *Sporting injuries*

Pursuit	*No.*	*Gls*	*Pursuit*	*No.*	*Gls*
Darts	4	0	Fishing	2	0
Squash	5	5	Hurling	1	0
Shooting	4	0	Cricket	1	1
Golf	2	1			

Gls denotes number of injuries caused by broken spectacles.

Table 7 *Industrial injuries*

Using hammer	43 (23 using a chisel)
Operating machine	15
Using: screwdriver	5
knife	5
wire	4
drill	3
nail punch	2
Grit/stone/coal	4
Miscellaneous	28

Table 8 *Domestic injuries*

DIY	29 (13 IOFBs, 7 hammer and chisel)
Fall	14 (1 faint and 1 fit)
Glass	13 (5 exploding bottles)
Car/bike repairs	6
Blunt injury	4 (stone/brick)
Gardening	2
Home brewing	2
Miscellaneous	
Dog bite	1
Pen	1
Knife	1
Record	1
Plate	1
Fingernail	1
Unknown	1
Walking on rubbish tip	1

DIY='do it yourself' domestic repairs.
IOFB=intraocular foreign body.

Table 9 *Childhood injuries*

Dart	11
Blunt objects	8 (stone, brick, football, heel, knee)
Knife	8
Pen/pencil	7
Wood/stick	7
Glass/bottle/cup	5
Plastic fragment	4
Hammering	4 (chisel, brick, bullet, cartridge)
Air gun	3
Garden (bushes, etc)	3
Wire	2
Pliers/tweezers	2
Bicycle repair	2
Ruler/measure	2
Spike/nail	2
Exploding bottle	1
Spotlight	1
Chisel	1
Stitch cutter	1
Swimming goggles	1
Fish hook	1
Napkin pin	1
Compasses	1

In four of these cases the injury was caused by the flight end entering the eye.

Discussion

Although all eye injuries should be preventable, attempting to reduce their incidence is fraught with problems.[2] Factors which can affect the pattern of eye injuries include changes in both population and environment. Preventive measures taken are influenced by social conscience as well as economic considerations.[3]

The age and sex distributions showed a similar pattern to those of previous series.[4-6] We found a lower percentage of eye injuries in the under 9 age group (Table 2). The male preponderance was greater in this series (7·8:1) than in Eagling's[6] study (3·5:1).

There were six cases of endophthalmitis (1·6%). Five of these were excised and one was retained, albeit with no perception of light. Two cases of endophthalmitis were associated with intraocular steel foreign bodies from hammering. Although these injuries are thought to be sterile, all possible precautions to prevent intraocular infection should still be taken.

There was one recorded case of sympathetic ophthalmitis. It occurred in a child who had injured her eye (scleral perforation with uveal prolapse) with a pair of compasses two weeks prior to presentation.

ROAD TRAFFIC ACCIDENTS

In all four regions the reduction in injury due to RTAs before and after the seat belt law was demonstrated clearly. Initially it was puzzling why Sheffield should have so few RTA cases, but Rotherham and Chesterfield Hospitals are closer to the motorway network, and this influenced Sheffield's intake of them. The reduction in RTA-induced perforating eye injuries after the seat belt law in Hampshire was analysed by Hall.[1] We have confirmed that his conclusions are widespread and consistent. The estimated annual incidence has decreased by 76.9% and is comparable to the figure obtained in the Hampshire study (73%) RTAs predominantly affected the young. The number of working days lost, the cost to the NHS, and the cost in terms of visual handicap have been reviewed elsewhere.[7] There were four cases of double perforations in the series, of which two were due to RTAs. This is to be expected in view of the head trajectory through a windscreen.[7]

In this series the position of the injured patient in the motor vehicle was reviewed. Front seat passengers were more commonly affected than back seat. The driver has a moral responsibility for the safety of his passengers, and it may still be important to publicise this. We found the incidence of eye injury in back seat passengers to be very low. One of the three cases resulted from flying glass. It is not known how the other two suffered their injuries. In our opinion these figures hardly justify encouraging the introduction of seat belt legislation for back seat passengers.

Out of the 37 cases in which a clear history was obtained 31 admitted that they were not wearing their seat belts. One patient who was wearing a seat belt thought that it may not have been fastened. If these histories are correct, the wearing of a seat belt does not provide complete protection from eye injury. For example, in one instance the accident was so severe that the roof of the car was ripped off completely. In another case the belt apparently caused the patient's glasses to smash and perforate the eye, which seems hard to believe unless the belt was worn incorrectly. Despite imposition of the law, RTA-induced perforating eye injuries still occur. We must continue to encourage the wearing of seat belts.

ASSAULT CASES

We recorded a higher ratio and number of assault cases than in Roper-Hall's series[4] in the 1950s (11·1% against 0·75%). Birmingham was not thought to be a violent city, but even so its incidence of assault in this study was 7·7%. Liverpool (13·1%) and Manchester (13·4%) had a higher incidence of assault cases and may reflect more unsettled social environments.

We discovered that 22 cases were of patients injured by a broken glass or bottle in or near a pub or club. The problem of glass breakage has been the subject of research for many years.[8] Not only are we a long way from obtaining an unbreakable glass technically, but toughened glass of any kind is much more expensive and not yet cost effective. For large sporting occasions, plastic and paper have been used in place of the traditional drinking glass. There are no signs of this becoming more widely acceptable to the general public.

It should be possible to identify those pubs and clubs with a high incidence of glass injuries. However, the idea of imposing restrictions in the use of glass in these establishments was not met with enthusiasm by the Health and Safety Committee for the Brewers' Society (personal communication). They regard acts of such a malicious nature as being beyond their responsibility and out of their control. The tougher penalties recently imposed by the courts of law are welcomed.

SPORTING INJURIES

The most common sport associated with penetrating eye injury was squash racquets. Despite attempts to encourage the use of plastic lenses or contact lenses in sportsmen and women, all five of our squash related injuries resulted from the wearing of glasses which shattered on impact. Sports clubs could help to reduce the incidence by introducing rules forbidding the use of glass spectacle lenses.

OCCUPATIONAL INJURIES

Hammer and chisel injuries were found to be most common. Fifteen machine operators suffered perforating injuries. The difficulty in encouraging the use of protective goggles has been discussed.[2] Manchester had a much lower incidence of industrial injuries than the other centres, particularly Sheffield. This may be related to the type of industry prominent in each region.

DOMESTIC INJURIES

Thirteen cases in the DIY subgroup were due to hammering (mostly with chisels). There was only one case resulting from chopping wood, an occupation previously common, with a traditionally high ocular morbidity.[2] Four cases were caused by exploding bottles; this subject has been reviewed elsewhere.[9] Apart from these, no notable subgroups emerged.

CHILDHOOD INJURIES

Dart injuries are the largest subgroup. The most common mode of injury described was the flight end entering the eye while the player was pulling the dart out of the board (five cases). Four cases were associated with the dart bouncing off the board. The severity of these injuries could be minimised by altering the design of both dart and board. Parents should be made aware of their potential dangers.

Educational programmes on the prevention of accidents in the home have been used in the past and should be encouraged. Apart from the dart subgroup, the wide variety of objects responsible makes it difficult to pinpoint a group on which a publicity campaign could concentrate.

CONCLUSION

This study has confirmed the effectiveness of the seat belt law as a preventive measure in reducing serious ocular morbidity. Assault cases are becoming more frequent. They are caused most commonly by a broken glass or bottle. Although these injuries could be reduced by replacing drinking glasses with plastic or paper, this seems impracticable. Using plastic lenses in spectacles would reduce the number of sporting injuries. Dart injuries in children are common, and parents should be encouraged to show caution with darts in the home. We must continue to review eye trauma to identify repeated patterns of injury. These may then be influenced by justifiable and acceptable legislation or increasing public awareness.

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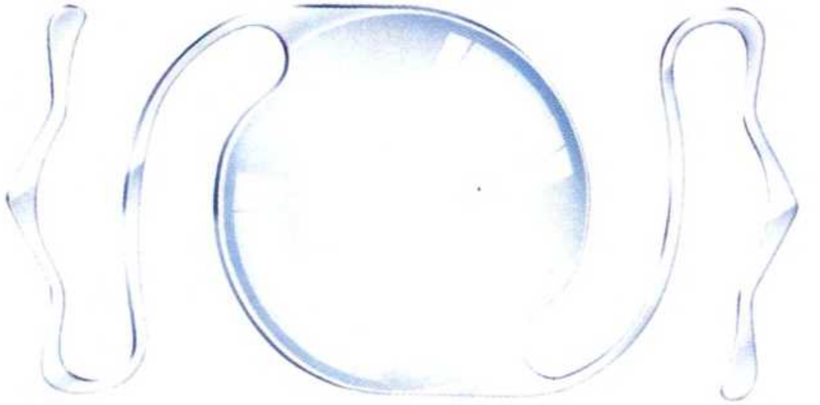

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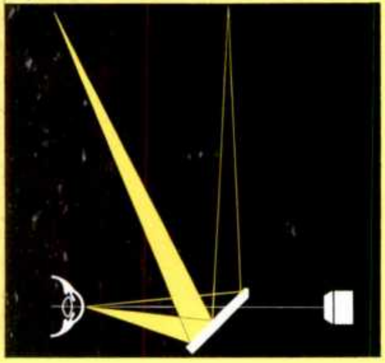

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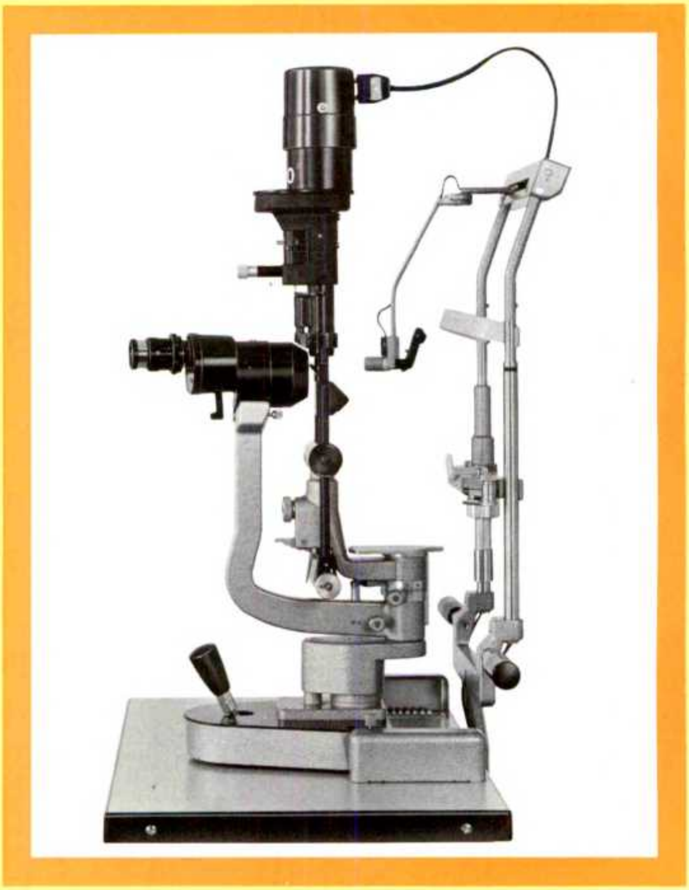

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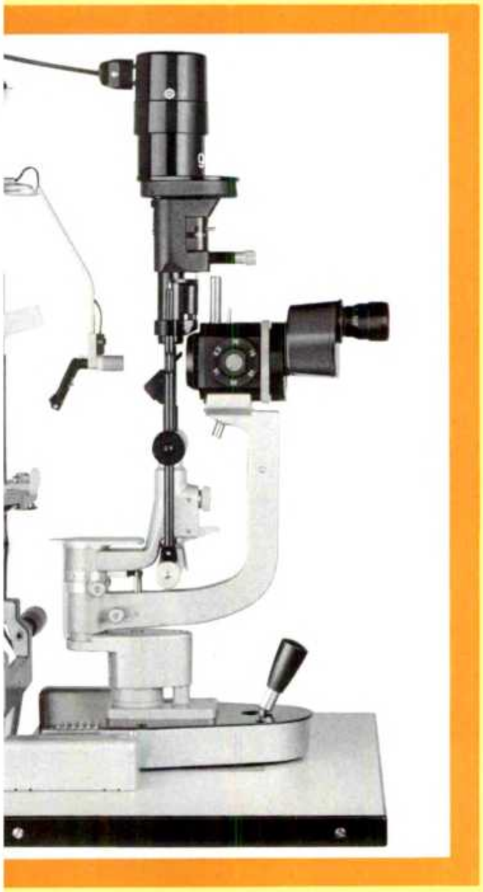

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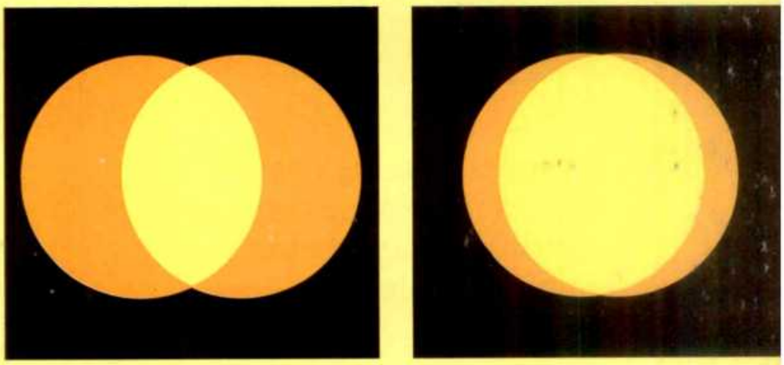

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British Journal of Ophthalmology, 1987, **71**, 441–444

Neodymium-YAG transscleral cyclocoagulation in rabbit eyes

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SUMMARY Transscleral ruby cyclocoagulation has been successfully used to lower intraocular pressure. The recent commercial availability of Nd-YAG lasers with a thermal mode provides a possible alternative by which to perform this procedure. We treated one eye of seven pigmented rabbits using the thermal mode of the Nd-YAG laser. The intraocular pressures were followed up for three months. The treated eyes had significantly lower mean intraocular pressures than the untreated contralateral eyes ($p<0{\cdot}001$). Moreover, the decrease was sustained over the three-month duration of the study. Pathological examination revealed very selective destruction of the ciliary processes, with sparing of the overlying ciliary muscle, sclera, and conjunctiva. The potential value of this mode of therapy for use in patients with glaucoma is discussed.

Transscleral ruby laser cyclocoagulation was first used by Beckman and colleagues[1 2] to lower intraocular pressure (IOP). Owing to the lack of general availability of such lasers this technique has not been much used clinically over the years.

Neodymium-yttrium-aluminium-garnet (Nd-YAG) lasers have recently become commercially available. These lasers provide a possible alternative by which transscleral ablation of the ciliary processes can be performed.

Nd-YAG lasers (along with ruby lasers) are pulsed lasers. They emit light in the infrared region of the spectrum (wavelength 1064 nm). The duration of the emitted pulse is in the millisecond range ('free-running' or 'thermal mode'). If a Q-switch or mode-lock shutter is used, the pulse duration is reduced into the nanosecond or picosecond range respectively, with power levels of several hundred thousand watts. With such enormous power levels electrons, rather than being absorbed, are stripped off molecules and atoms, causing plasma formation (a mixture of ions and free electrons).[3]

In contrast, when used in the thermal mode, the infrared pulses are prolonged, and therefore the laser has a much lower power output (100–200 W). Since the infrared wavelengths are in the invisible portion of the spectrum, the absorption properties are very different from those of conventional argon or krypton lasers. The infrared energy has been shown to penetrate six times more deeply into tissues than that of the argon laser before being absorbed.[4] The infrared energy can thus penetrate the scleral wall before producing a thermal reaction in the region of the ciliary processes.

The purpose of this study was, firstly, to investigate whether transscleral treatment with the thermal mode of the Nd-YAG laser can decrease the intraocular pressure (IOP) in pigmented rabbits over a three-month period, and secondly to study the sclera and ciliary processes histologically to determine the effects of this form of treatment.

Methods and materials

Seven pigmented rabbits weighing 2–3 kg were used in the study. The animals were anaesthetised with sodium pentobarbital injected intravenously into an ear vein. One eye of each animal was randomly selected to be treated with the laser. The untreated eye served as the control.

Each treated eye received 24 burns by the thermal mode of the Lasag MR 2 Nd-YAG laser (Fig. 1). The laser burns were placed 1 mm posterior to the limbus, with a pulse duration of 20 ms, at a pulse energy of 2 joules (resultant power 100 W). The aiming beam

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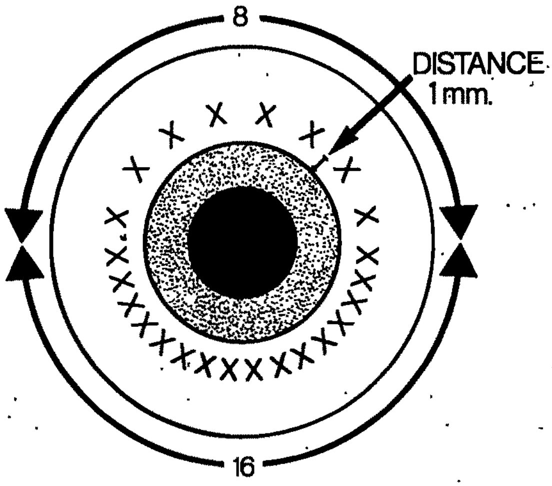


Fig. 1 *Location and number of Nd-YAG laser burns in relation to the limbus.*

was focused on the conjunctiva, but the laser was offset 2·4 mm (offset 6 on the Lasag) in order to treat the ciliary processes selectively.

One animal died immediately after laser treatment as a complication of general anaesthesia. The treated eye was submitted for pathological examination.

The remaining six animals had daily IOP measurements for the first three weeks, and then weekly IOP measurements for a total of three months. Intraocular pressure measurements were performed in a masked fashion with a Perkins hand-held applanation tonometer.[5] The pressure measurements were performed at 0700 daily, with the animals awake, with local anaesthesia by topical proparacaine hydrochloride 0·5% over a three-month period. One drop of Maxitrol (dexamethasone 0·1%, polymixin B, neomycin) was instilled into both eyes for the first three weeks of the study.

One of the animals had to be destroyed after four days because of a broken hind leg. The treated eye from this animal was also sent for pathological examination. At the end of three months the remaining five rabbits were killed and their eyes were examined histologically.

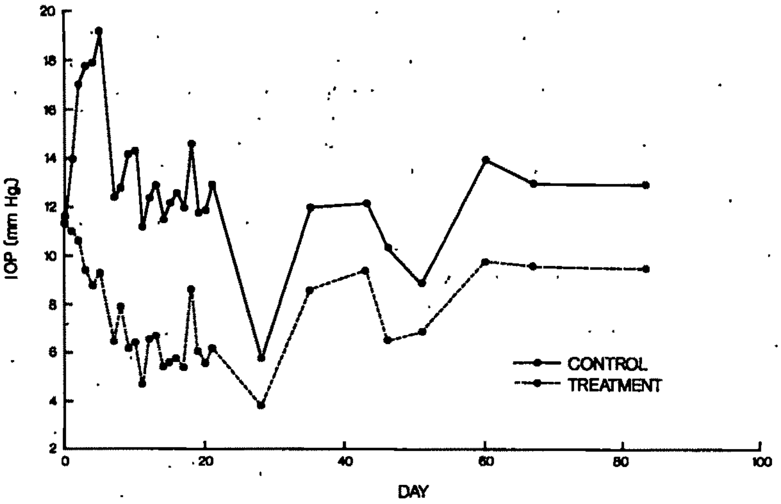
Results

Three of the six treated eyes developed hyphaemas, ranging from 20% to approximately 80%. All these hyphaemas disappeared without apparent consequence within two weeks. Moderate conjunctival injection was present in all treated eyes for the first week.

Analysis of variance was used to compare the treated and control eyes. Nd-YAG laser treatment was found to significantly lower the IOP in the treated eyes ($p<0·001$). Furthermore the difference between the treated and control eyes over the three-month course of the study showed no statistically significant change ($p>0·7$). In other words the IOP lowering effect of the laser treatment showed no tendency to diminish over the three-month period of observation. Fig. 2 charts the effect of the Nd-YAG laser cyclocoagulation on rabbit IOPs. Each point represents the mean of three readings.

All treated eyes showed areas of depigmentation of ciliary epithelium on gross examination, without any evidence of damage to the exterior scleral surface. Pigment dispersion was more diffuse in animals examined at three months in contrast to the localised burn depigmentation in the animal which

Fig. 2 *Mean IOP values after Nd-YAG therapy.*



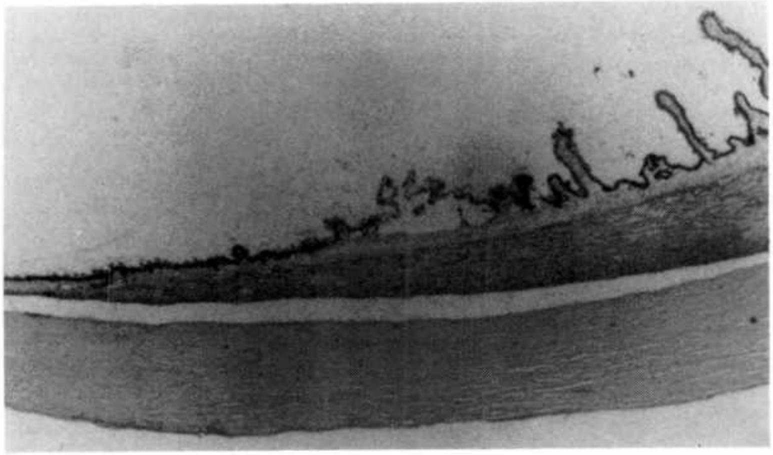


Fig. 3 *Histological examination of laser burns 24 hours after treatment, showing 'blistering' of pigmented ciliary epithelium with surrounding mild oedema. Haematoxylin and eosin.*

died shortly after its laser treatment. Histological examination of this animal showed a 'blistering' effect on the pigmented ciliary epithelium, which was lifted off the stroma, showing oedema in the immediate area (Fig. 3). The ciliary muscle fibres appeared to be intact, as did sclera.

The animals examined at three months showed a variety of changes depending on the location of the burn. The usual change was dispersion of pigment and fibrosis, with some atrophy of ciliary muscle fibres in the immediate area of the burn (Fig. 4). The animals that bled had so much haemorrhagic necrosis that the laser burns were obscured.

Discussion

Beckman and colleagues[1 2] successfully used a specially designed ruby laser for transscleral cyclocoagulation during the early 1970s. Wilensky *et al.*[6] have recently shown that transscleral cyclocoagulation lowers IOP in pigmented rabbits, using the thermal mode of the Nd-YAG laser. Their results suggested that the higher energy levels (1·5–2·0 J) may be successful in producing a sustained lowering of the IOP. Our study confirms this effect. The treatment parameters and follow-up time used in our study, however, were different from those of Wilensky *et al.* We used a relatively high energy level (2 J) but with a 20 ms pulse duration rather than 10 ms. The resultant power was therefore 100 W rather than 200 W. Our animals were all followed up for a period of three months, against a maximum of 48 days follow-up in the other study. We also set the laser on 2·4 mm 'Offset' so as selectively to destroy

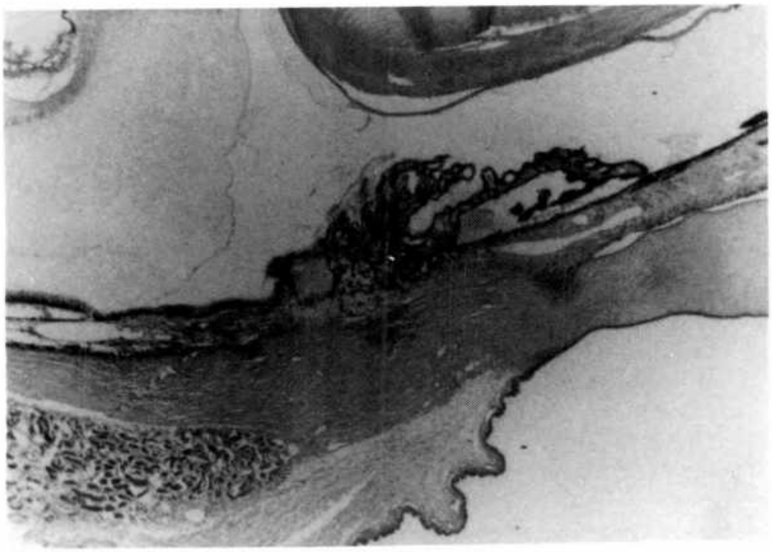


Fig. 4 *Histological examination of laser burn three months after treatment, showing pigment dispersion and fibrosis in the ciliary processes. Haematoxylin and eosin.*

the ciliary body and processes, unlike the other study. With these modes of treatment the IOP was decreased in all treated eyes for the duration of the study.

The presumed mechanism of action of this technique is decreased aqueous production secondary to destruction of the ciliary processes. Pathological examination of the treated eyes showed that, with our technique, the sclera was not affected, with the laser being very successfully focused on the ciliary processes. The only observed side effects in this study was a self resorbing hyphaema in 50% of the treated eyes.

Although the treatment appeared to be effective in lowering normal IOPs in rabbits, further studies are required to investigate the efficacy of this mode of treatment in humans with glaucoma. Cyrlin *et al.*[7] have published preliminary results on human eyes. It appears that the technique is indeed of potential value in cases of uncontrolled IOP.

The recent availability of Nd-YAG lasers with the thermal mode option has created a widely available source of pulsed laser energy. Our results on rabbit eyes, taken in conjunction with preliminary results on human eyes, suggests that Nd-YAG cyclocoagulation may prove to be a new tool in the management of various types of glaucoma.

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Development of an isolated retinal macroaneurysm of the cilioretinal artery

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SUMMARY A case of isolated retinal macroaneurysm showed interesting features. First, it involved a cilioretinal artery, which is a rare site; secondly, its development was preceded by vessel changes characterised by hyalinisation and permeability of the arterial wall.

Isolated retinal macroaneurysms are acquired dilatations of the major branches of the central retinal artery.[1] They are found in subjects with vasculopathies, especially arterial hypertension and arteriosclerosis.[1-5] Frequently macroaneurysms produce complications such as oedema, retinal, subretinal and vitreous haemorrhages, and serous detachment of the retina, generally in the posterior pole.[2 3 5 6] The pathogenesis of macroaneurysms is not well known and the vessel abnormalities that precede their development have rarely been demonstrated.[7]

We have followed the development of a macroaneurysm located in a cilioretinal artery, a very rare occurrence, and have observed some interesting changes in the arterial wall heralding the formation of the macroaneurysm. The recognition of these changes could be important in the selection of patients at risk of developing macroaneurysms.

Case report

A 70-year-old woman complaining of a bilateral decrease in visual acuity was referred on 27 August 1983 to our service of fluorescein angiography with a diagnosis of hypertensive retinopathy. She had suffered from arterial hypertension for many years; her therapy included hydrochlorothiazide, alphamethyldopa, and platelet anti-aggregating drugs. At the time of the visit her blood pressure was 180/100 mmHg. A slight increase in plasma lipids (cholesterol 8·5 mmol/l; triglicerides 3·2 mmol/l) was found.

The corrected visual acuity was 20/40 in the right eye and 20/200 in the left eye. There was an early nuclear cataract in the right eye and a more advanced nuclear and posterior subcapsular cataract in the left eye.

Examination of the fundus of the right eye showed narrowing of the retinal arteries and compression at arteriovenous crossings. Some tracts of the nasal and superotemporal arteries were hyalinised, and along their course there were some round haemorrhages. A macular cilioretinal artery was hyalinised and surrounded by some hard exudates in its supramacular tract (Fig. 1). A chorioretinal scar was seen in the superotemporal fundus, and some small haemorrhages and hard exudates were observed in the macula. The fundus of the left eye showed arterial narrowing, abnormal arteriovenous crossings, haemorrhages, and hard exudates in the posterior pole. There was neither hyalinisation nor occlusion of retinal arteries.

Fluorescein angiography in the right eye revealed occlusion of some branches of the nasal and superotemporal arteries. The cilioretinal artery was normally filled and in its hyalinised tract showed an irregular sausage-like dilatation (Fig. 2). There was no leakage.

On 20 April 1984 the corrected visual acuity was 20/60 in the right eye and 20/200 in the left eye.

Occlusion of an inferotemporal branch of the central retinal vein occurred. Ischaemia and slight oedema of the macula were observed. The lesion of the cilioretinal artery was unchanged. The patient refused argon laser treatment of the affected area.

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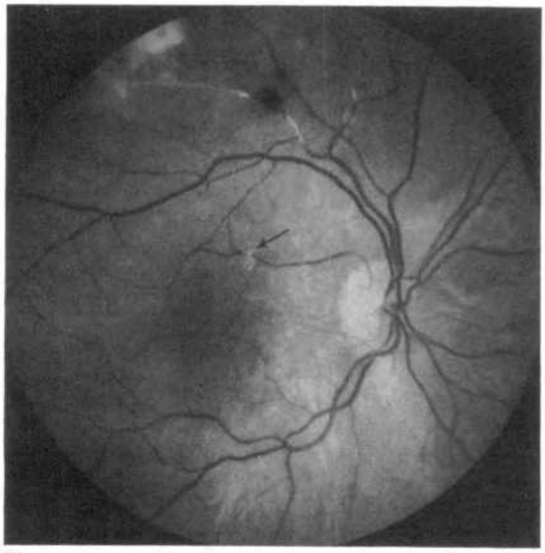

Fig. 1 *A tract of the cilioretinal artery shows hyalinisation of the walls (arrow). Below it are some hard exudates. The superotemporal branch of the central retinal artery is partially hyalinised.*

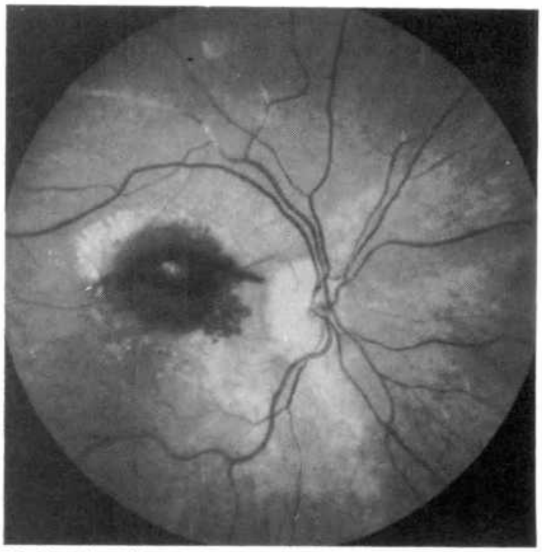

Fig. 3 *The cilioretinal artery shows a macroaneurysm covered by a preretinal hemorrhage. In the same area a ring of hard exudates and a subretinal haemorrhage are seen.*

At the next examination, on 10 April 1986, the patient's blood pressure was 170/100 mmHg and normal serum lipids. The visual acuity was the same as that found previously.

Along the cilioretinal artery, in the macula, there was a round, whitish ectasia, partly covered by a preretinal haemorrhage (Fig. 3). In the same area of the fundus a subretinal haemorrhage and a ring of hard exudates were seen.

Fluorescein angiography showed normal filling of the cilioretinal artery. The aneurysmal dilatation filled at the same time as the artery and showed leakage (Fig. 4). The patient again refused photocoagulation.

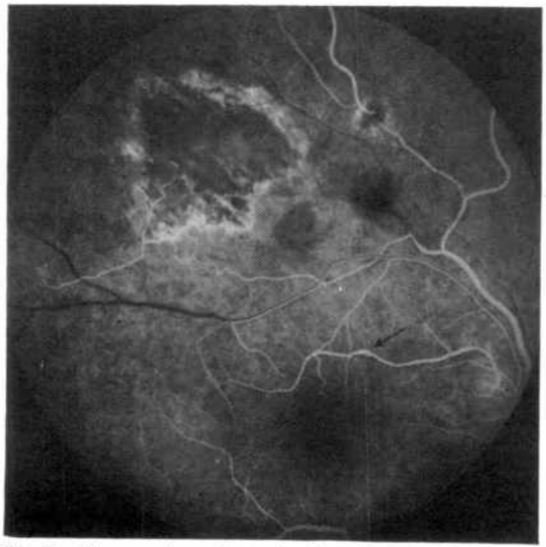

Fig. 2 *Fluorescein angiography demonstrates that the hyalinised tract of the cilioretinal artery is slightly dilated (arrow). The superotemporal artery incompletely fills owing to occlusion.*

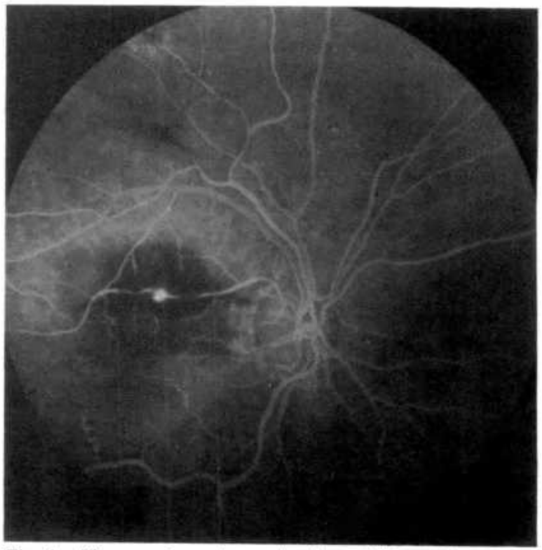

Fig. 4 *Fluorescein angiography shows filling of the cilioretinal artery and the macroaneurysm. There is leakage from the macroaneurysm.*

Discussion

The natural history of retinal macroaneurysms is not completely known. Much has been said about the evolution of macroaneurysms after they acquire the typical round appearance and cause haemorrhages and exudates. However, much less is known about the changes in the arteries which precede the development of the macroaneurysm. It is probable that the arteries from which the macroaneurysms arise are seriously compromised, for the patients are generally older than 60[2,4,5] and have hypertension and arteriosclerosis.[1-5]

Leishman[8] reported that retinal arteries of older people with arteriosclerosis show thickening of the vessel wall and loss of contractile elements that are replaced by collagen tissue. Arteries modified in such a manner might dilate owing to pressure increase, thus producing macroaneurysms. Lewis *et al.*[7] suggest that the production of macroaneurysms can follow focal damage of the vessel wall, especially at points where embolic plaques exist.

In the case described here we performed fundus photographs and fluorescein angiography before complete development of the macroaneurysm. In the tract where the macroaneurysm subsequently formed the artery showed slight enlargement, and its walls were hyalinised. Hyalinisation is a change that often accompanies arterial hypertension and develops in muscular arteries having a wall rich in collagen fibrils embedded in basal membrane-like material, as are the retinal arteries.[9] Furthermore, in our case there were abnormalities of the endothelium with breakdown of the blood-retinal barrier: this was revealed by the presence of hard exudates around the tract of the artery involved. However, the increase in permeability was not considerable, as the fluorescein angiography did not show leakage.

The study of this case leads one to believe that, at least in certain patients, the development of a macroaneurysm passes through an early subclinical phase characterised by moderate changes in the artery and a late phase characterised by gross anatomical abnormalities of the vessel, with oedematous and haemorrhagic complications.

The evolution of the macroaneurysm from the time when it produces these complications has been described.[2,6,10,11] The macroaneurysm can show involutional changes: the walls may sclerose and the lumen become occluded or remain open. In addition, the artery from which the macroaneurysm originates may become occluded, narrow, or maintain a normal lumen. Intraretinal haemorrhages become reabsorbed without sequelae, but subretinal haemorrhages can produce disciform scars. Oedema is a more serious complication of macroaneurysms and can cause cystoid degeneration of the macula when it settles in this area. It is important to note that, irrespective of the location of the macroaneurysm, the oedema, as in other retinal vascular disease like Coats's disease and von Hippel capillary haemangioma, tends to be localised in the macula.[12]

Some authors have suggested not treating the macroaneurysms that cause haemorrhages, but photocoagulating those that cause macular oedema.[5-7] If the macroaneurysm is small and far from the macula it can be directly photocoagulated; otherwise it is useful to perform photocoagulation all round the lesion.[4,5,13-15] Of course photocoagulation does not improve visual acuity if the oedema has already caused irreversible macular lesions.

As Robertson[1] stated, the location of the macroaneurysm is a retinal artery of the first three orders. Generally macroaneurysms are located in the superotemporal artery.[4,6,7,11] It is not clear, however, whether the higher frequency of macroaneurysms of the superotemporal artery is real or apparent, since a macroaneurysm at this site is apt to cause macular oedema and haemorrhages, with the consequent loss of vision that brings the patient to the ophthalmologist. Several macroaneurysms of the inferotemporal[4,12] and nasal[5,6] arteries have also been described. The case reported here, on the other hand, is one of the very rare cases of macroaneurysms of cilioretinal artery.[7]

The rarity of the location deserves some remarks. The cilioretinal artery is an artery of ciliary origin, while the retinal arteries arise from the central retinal artery. However, the haemodynamics of the ciliary arteries and retinal arteries are similar, in that their pressure are not much different. It is known that, in fluorescein angiography, the cilioretinal arteries fill together with, or often even before, the intraocular central retinal artery. The histological structure of the cilioretinal artery is the same as that of the first branches of the central retinal artery, consisting of a well developed muscular layer and a media and adventitia rich in collagen fibrils. It is understandable that the haemodynamic damage due to a hypertensive arterial disease could likewise involve the two arteries. Thus it is surprising that macroaneurysms of the cilioretinal artery are so much rarer than those of the central retinal artery despite an incidence of cilioretinal arteries in over 32% of the eyes in the general population.[16]

A possible explanation is that the greater length of the major branches of the intraocular central retinal artery as compared with the cilioretinal arteries could cause the former to be involved more frequently. Moreover, it is known that most macroaneurysms develop at arteriovenous crossings or where a vessel abruptly changes direction,[1,7] points where the endothelium and the muscularis are more subject to haemodynamic stress. Thus arteries that present a tortuous course, arteriovenous crossings, and many subdivisions, like the temporal branches of the central retinal artery, may be more prone to develop macroaneurysms than arteries having a straighter course, no arteriovenous crossings, and few branches, like the macular cilioretinal arteries.

Since macroaneurysms are not very rare complications in patients with arterial hypertension, and since they frequently threaten the macula, periodic photographic follow-up that shows changes in the arterial wall, such as hyalinisation, and increased vessel permeability may be useful in patients at risk. Such controls would allow the possibility of immediate photocoagulative therapy to prevent the development of oedema and subsequent irreversible macular lesions.

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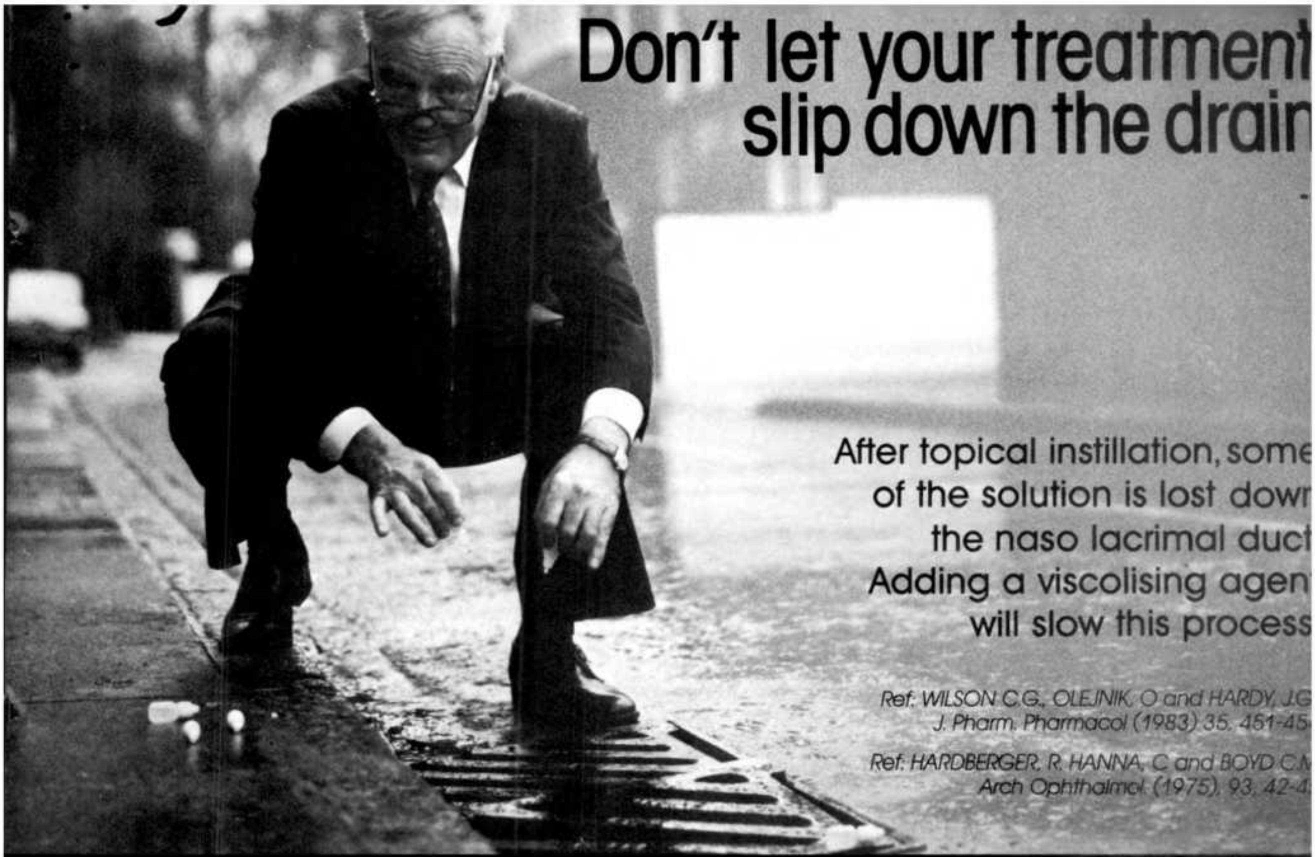

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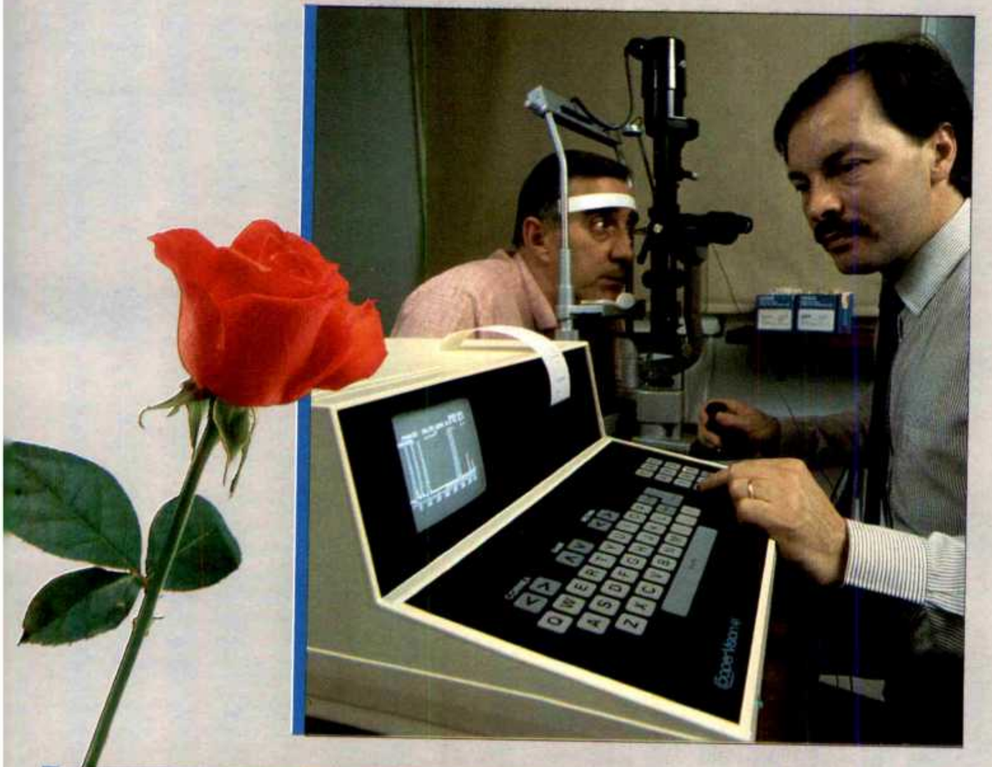

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British Journal of Ophthalmology, 1987, **71**, 449–453

A five-year survey of ocular shotgun injuries in Ireland

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SUMMARY Between November 1980 and September 1985 20 patients in Ireland sustained accidental ocular shotgun injuries severe enough to necessitate hospital admission. Eight patients had contusion injuries and 12 perforating injuries. Contusion damage was disproportionate to the size of the pellet. Through and through perforation of the globe occurred in eight patients; the remaining four patients in this group had retained intraocular pellets. Twelve patients sustained perforating eye injuries. Those that were treated by primary closure alone lost the sight in that eye. Those treated by vitreoretinal surgery recovered vision directly related to where the pellet had its exit from the eye. It was possible to contact 15 of the patients. All 15 were shooting pheasant. It was not possible to relate the distance of the patient from the gun to the severity of the ocular injury.

Accidental shotgun injuries regularly present to ophthalmic departments in Ireland. Over 176 000 shotgun licences were issued in Ireland in 1985, and game shooting is a popular sport. The injuries sustained have many distinctive features, contusion is severe, and the pellets travel towards the apex of the orbit. Perforation is common and often through and through. Vitreoretinal surgery is a prerequisite to satisfactory management of the perforating injuries. Two-thirds of the victims were shot by experienced gun handlers. Bullet and shrapnel injuries involving the eye have been extensively described by Duke-Elder,[1] and BB-gun injuries to the eye have been reported (a BB-gun is an air rifle that shoots pellets).[2 3] Bowen and Magauran[4] reported 105 cases of ocular injuries caused by airgun pellets. Conway *et al.*[5] mention the surgical management of two patients who suffered perforating eye injuries from shotgun pellets.

The regular presentation of ocular shotgun injuries to ophthalmologists in Ireland and the rarity of reports in the literature prompted this survey.

Material and methods

All ophthalmologists in the Republic of Ireland were circularised by letter. One of the authors (DR) telephoned each consultant, asking him if he could recall attending any patient involved in a shotgun accident during the period November 1980 to January 1985. Twenty patients were thus recalled. The charts were retrieved and scrutinised by the same author. Particular attention was paid to the ocular injury, its treatment, and ultimate best corrected visual acuity. Fifteen of the 20 patients were contacted about the circumstances of the accident. The age and experience of the person who shot them, the type of the gun and cartridge used, and the distance from the patient were ascertained. It was not possible to interview five patients as they could not be contacted.

Results

Twenty patients were involved in ocular shotgun accidents from November 1980 to January 1985—an average rate of four cases a year from a population of 3·8 million people. The findings of our survey are tabulated in Tables 1 and 2. Ten of the 20 patients (50%) presented in November, three (15%) in December, and four (20%) in January. All the patients were male, their ages ranging from 10 to 65 years, mean 30 years. Of the 20 patients three sustained bilateral eye injuries, accounting for 23 eyes. Thirteen of the 17 uniocular injuries (76%) were to the right eye.

Clinically the injuries were divided into two groups:

1. CONTUSION INJURIES

Eight patients had contusion eye injuries, one patient

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Table 1 *Patients with contusion injuries*

Case no.	*Date of presentation*	*Sex*	*Age*	*Eye*	*Injuries*	*Management*	*Ultimate visual acuity*	*Interviewed*	*Target, circumstances, distance*	*Gun handler, age, sex, relationship to patient, experience*
1	2 Nov 1980	M	42	R	Comotio retinae	Laser photocoagulation	6/9	Yes	Pheasant, sallies, 12 yards	15, M, acquaintance, no experience
2	2 Nov 1982	M	33	R	Comotio retinae	Conservative	6/6	Yes	Pheasant, ditch, 60 yards	25, M, brother, experienced
3	20 Nov 1983	M	30	L	Comotio retinae	Conservative	6/6	Yes	Pheasant, bush, 60 yards	32, M, relative, no experience
4	20 Jan 1983	M	20	L	III palsy	Conservative	6/9	Yes	Pheasant, ditch, 15 yards	35, M, friend, experienced
5	3 Nov 1984	M	19	R	Hyphaema+comotio retinae	Conservative	6/6	Yes	Pheasant, field, 60 yards	19, M, friend, experienced
				L	Eyelid entry wound	Conservative	6/6			
6	8 Jan 1984	M	29	R	III, IV, V, VI palsy	Conservative	6/12	Yes	Pheasant, ditch, 15 yards	35, M, acquaintance, experienced
7	21 Jan 1984	M	16	R	Comotio retinae	Conservative	6/6	Yes	Pheasant, field, 20 yards	23, M, brother, experienced
8	18 Jan 1985	M	25	R	Comotio retinae	Conservative	6/5	Yes	Pheasant, ditch	19, M, friend, no experience

Metric conversion: 10 yards=9 m.

had bilateral injuries, Table 1. In no case did a perforation occur in this group. In contusion injuries the pellet lodged in the retro-orbital tissue or in the cavernous sinuses. Contusion injuries included peri-orbital entry wounds, subconjunctival lacerations, and haemorrhages, hyphaema, comotio retinae, and transient vitreous haemorrhage (Fig. 1). In two cases (Nos. 4 and 6) the patients suffered transient cranial

Table 2 *Patients with perforating injuries*

Case no.	*Date of presentation*	*Sex*	*Age*	*Eye*	*Injuries*	*Management*	*Ultimate visual acuity*	*Interviewed*	*Target, circumstances, distance*	*Gun handler, age, sex, relationship to patient, experience*
9	2 Nov 1980	M	59	L	Double perforation with RD	1° Closure	HM	Yes	Pheasant, field, 100 yards	55, M, friend, experienced
10	4 Dec 1980	M	45	R	Single perforation, phthisical	1° Closure	NPL	No response		
11	4 Jan 1981	M	29	R	Double perforation, phthisical	1° Closure	NPL	Yes	Rabbit, ditch, 10 yards	33, M, brother, experienced
12	12 Nov 1982	M	65	L	Double perforation, vit. haem. RD	1° Closure	HM	Yes	Pheasant, 20 yards	33, M, friend, no experience
13	13 Nov 1982	M	15	R	Double perforation, phthisical	1° Closure	NPL	Yes	Pheasant, field, 30 yards	45, M, no experience
14	6 May 1983	M	?	R	Double perforation, phthisical	1° Closure	NPL	No response		
15	22 Aug 1983	M	29	R	Double, aphakia	1° Closure + vitrectomy	6/9	No response	Family feud	
				L	Single, aphakia	1° Closure + vitrectomy	CF			
16	4 Nov 1983	M	14	R	Single, vit. haem.	1° Closure + vitrectomy	6/12	No response		
17	27 Dec 1983	M	40	R	Double perforation, phthisical	1° Closure + vitrectomy	NPL	Yes	Woodcock, ditch, 60 yards	45, M, uncle, experienced
18	5 Nov 1983	M	25	R	Double, aphakia, vit. haem.	1° Closure + vitrectomy	6/60			
19	17 Nov 1984	M	10	R	Single, phthisical	1° Closure	NPL	Yes	Pheasant, ditch, 30 yards	21, M, brother
20	4 Dec 1984	M	24	R	Double, vit. haem., aphakia	Vitrectomy	2/60	Yes	Pheasant, ditch, 15 yards	34, M, friend, experienced
				L	Double, vit. haem., aphakia	Vitrectomy	6/9			

CF=counting fingers. HM=hand movements. NPL=no perception of light.

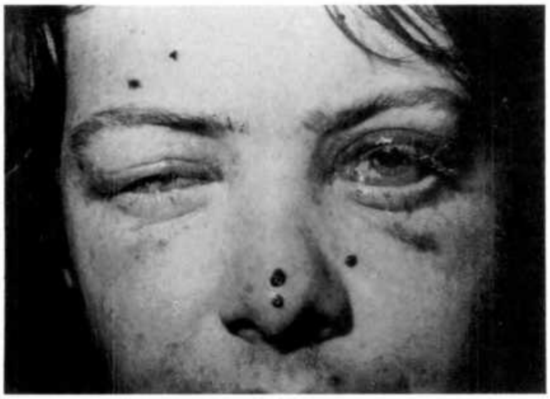

Fig. 1 *Typical presentation of a patient with shotgun injuries.*

nerve palsies, which recovered within three months. All of the contusion injuries were managed conservatively. There was no attempt to remove the pellets unless they were palpably superficial.

In all nine eyes the visual acuity recovered to 6/12 or better without surgical intervention. Two years after the initial injury a retinal tear developed in case 1. This was satisfactorily treated by laser photocoagulation.

2. PERFORATING INJURIES

Twelve patients had perforating eye injuries and two of these were bilateral, so that there were 14 eyes in this group (Table 2). In four eyes the pellet was retained within the globe; in the other 10 a double perforation occurred, and the pellet had its exit posteriorly from the globe into the orbit. The entry wound was either corneal, limbal, or scleral anterior to the equator (Fig. 2). Hyphaema, cataract, and vitreous haemorrhage obscured the exit site until vitreoretinal repair cleared the visual media. Seven of the 14 eyes were managed by primary closure of the entry site alone. Five of these never recovered any sight and progressed to phthisis bulbi; two had hand movement vision.

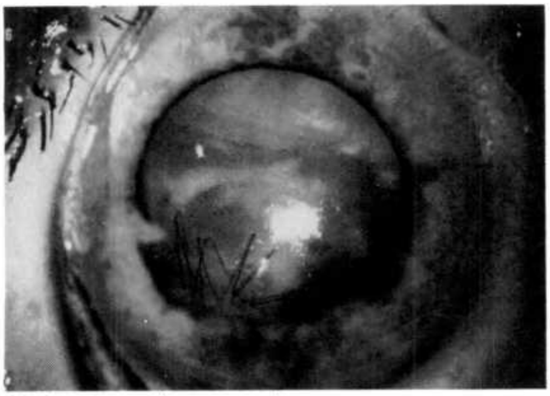

Fig. 2 *A corneal entry wound.*

The remaining seven cases were treated by vitreoretinal surgery within a week of primary closure of the entry wound. Three cases recovered a visual acuity of 6/12 or better, one case 6/60, one 2/60, one counting fingers, and one no perception of light, with phthisis bulbi.

Fifteen of the 20 patients were interviewed. All were shot by accident while shooting pheasant. Nine of the 15 patients (60%) stated that there was a ditch or hedge between themselves and the person who accidentally shot them. The range of fire varied from 10 to 100 yards (90 m) with an average range of 38 yards (35 m).

Both hunters and patients were male. Four of the 15 people were shot by their brothers. They were aged between 15 and 55 and averaged 33 years. In the patients' own estimation 10 of 15 people (66%) had good experience with shotguns, while five of 15 (33%) had no or very little experience. The gun used was usually a 12 bore double barrel shotgun with a No. 5 or 6 cartridge.

Discussion

Accidental ocular shotgun injuries are a regular occurrence during the shooting season. This study revealed on average four new cases each year. Accidents occurred mainly in November, 50% in our series. November is the first month of the pheasant shooting season. Awareness by the hunters and particular caution at the start of the season may reduce this incidence.

Contusion injuries are treated conservatively, but there is risk of a late retinal detachment. The visual prognosis in these cases was good—6/12 or better. In two cases (Nos. 4 and 6) there were transient cranial nerve palsies. The pellet in both cases entered the orbit medial to the globe, and a CT scan showed the pellet in the cavernous sinus. The pellets were left in situ and both patients made full neurological recovery within three months of the injury. Contusion injury is disproportionately much greater than the size of the pellet.

Pellet toxicity has been considered by Bowen and Magauran.[4] They measured blood and urine lead levels in four patients with retained intraorbital pellets. These values remained within normal values up to six years after the injury. All postseptal pellets have been left in situ in our series of patients without ill effect.

Perforation of the globe was the most serious result of a shotgun injury. These perforations are sometimes single, often double, and were characterised by

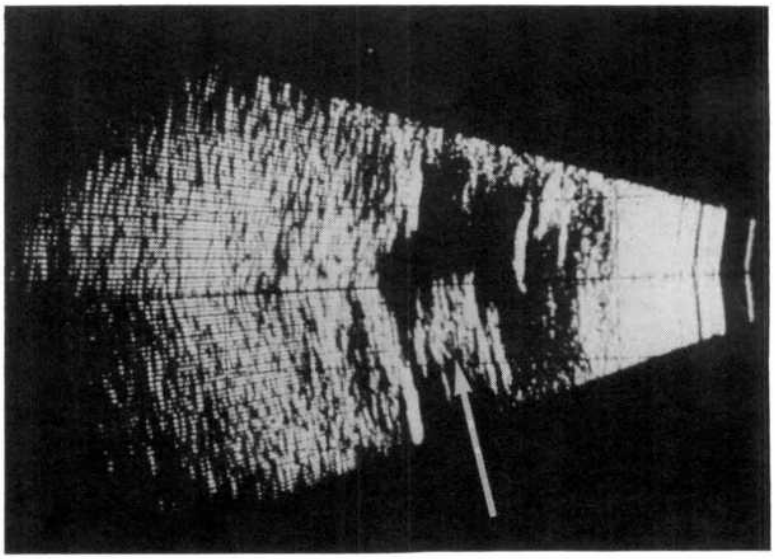

Fig. 3 *Ultrasonographic demonstration of an intravitreal haemorrhage (arrow) in a patient with a double perforating injury.*

intraocular haemorrhage (Fig. 3), vitreous incarceration, and a possible retinal detachment. It has been shown experimentally[6 7] and it is recognised clinically[8] that perforating injuries (with these complications) have poor prognosis when treated by conventional techniques. In this study seven eyes were treated by primary closure alone and none recovered useful vision, with the development of phthisis in five. In contrast, the seven eyes treated by vitrectomy within one week of primary closure had a much more favourable visual outcome. Three of the seven regained a visual acuity of 6/12 or better, and in the other four the eye was salvaged but the visual potential had been destroyed by the pellet leaving the eye at or near the macula.

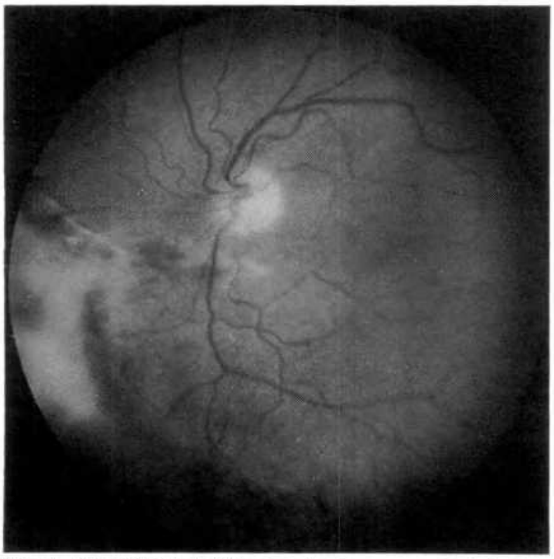

Fig. 4 *Case 20. The left fundus showing an equatorial exit. The visual acuity is 6/9.*

Perforating injuries involving the posterior segment result in vitreous gel incarceration and vitreous haemorrhage. This progresses to retinal traction and tractional retinal detachments. In those cases which underwent vitrectomy we consider the scaffolding on which the contractile fibroblasts proliferate was removed, aborting the retinal traction and detachment and salvaging the visual potential of the eye.

It has been suggested previously that visual outcome may be related to the entry site of the pellet.[9] In our series the visual outcome was related to where the pellet had its exit from the globe. In the two bilateral perforation injuries (cases 15 and 16) the visual acuity was 6/9 where the pellet had its exit at the equator (Fig. 4). In contrast, the visual acuity was counting fingers and 2/60 when the pellet left the eye at or near the macula (Fig. 5).

Fifteen of the 20 patients were interviewed, nine of them described the accident occurring through a ditch or hedge. We found no correlation between the severity of the injury and the distance from which they were shot. Indeed one case (No. 9) was shot from 100 yards (90 m). He had a double perforation and the eye was lost. He received no other injuries. It is noteworthy that 10 of the 15 were shot by people who, in the patients' estimation, were experienced.

In conclusion, the results in this study suggests that, after a shotgun injury, contusion eye injuries are best treated conservatively. But eyes with perfor-

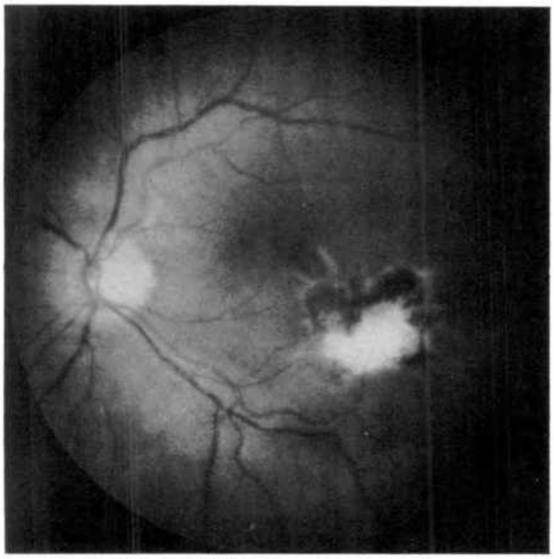

Fig. 5 *Case 15. The left fundus showing a paramacula exit. The visual acuity is CF.*

ating injuries should, after primary closure, be considered for early vitrectomy in the presence of significant intraocular haemorrhage and/or retinal detachment. In the assessment of these cases ophthalmic ultrasound is of particular value.

By publicising the risk of these injuries to gun clubs and other interested parties the incidence of these avoidable, serious ocular injuries may be reduced. We are unable to make any additional recommendations to the safety standards already obtaining.

The authors acknowledge with gratitude the co-operation of ophthalmologists in Ireland in providing us with the patients for this survey.

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Vitreoretinal junction in infectious endophthalmitis in a primate eye

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SUMMARY A primate eye affected by postoperative infectious endophthalmitis was studied early in the course of the disease. Retinal perivasculitis, vitreoretinal adhesions along the inflamed vessels, and traction of the partially separated posterior vitreous on the retina at the adhesion sites were observed. It is suggested that such vitreoretinal junction pathology may be responsible for the development of retinal detachment in infectious endophthalmitis.

Endophthalmitis is a devastating complication of intraocular surgery and penetrating eye injury. In spite of modern management, which includes intravitreal injection of antibiotics and steroids,[1] and vitrectomy,[2,3] a considerable number of affected eyes are lost.

One of the more ominous sequelae of endophthalmitis is retinal detachment, which is believed to be tractional or exudative[4,5] or rhegmatogenous.[6] A strikingly high incidence of retinal detachment was recently found in a series of cases of post-traumatic endophthalmitis (Jarus G, personal communication, 1984). The exact pathogenesis of the detachment, however, is difficult to prove, since the affected eyes reach the pathologist as disorganised tissue after evisceration or late in the course of the disease as a phthisical eye.

We recently had the opportunity to study a primate eye early in the course of infectious endophthalmitis. We now present the gross and microscopic pathological changes of the vitreoretinal interface of this eye and propose that they may explain the pathogenesis of endophthalmitis-related retinal detachment.

Material and methods

An adult cynomolgus monkey developed endophthalmitis of the right eye following an unsuccessful attempt to inject gas into the vitreous cavity; all the gas immediately leaked out of the eye through the injection site. Twenty-four hours later the eye was congested and chemotic, and haziness developed in the cornea, anterior chamber, and vitreous. In spite of intensive topical as well as subconjunctival antibiotic treatment, hypopyon and yellow vitreous exudates followed and within three days obscured the

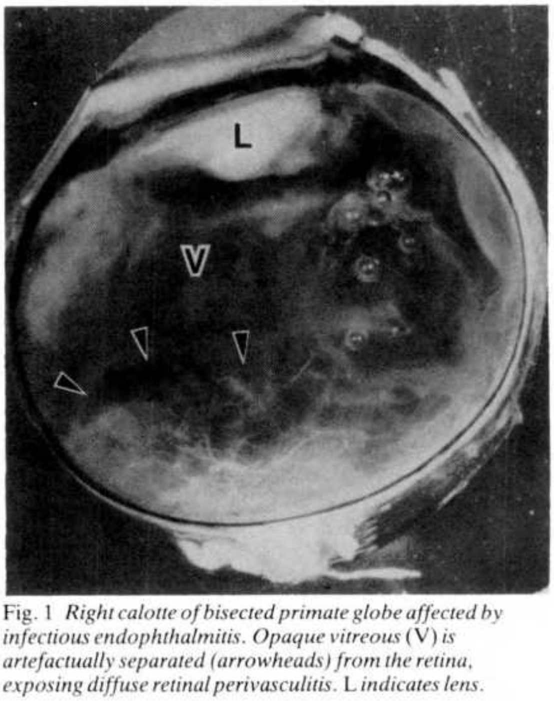

Fig. 1 *Right calotte of bisected primate globe affected by infectious endophthalmitis. Opaque vitreous* (V) *is artefactually separated (arrowheads) from the retina, exposing diffuse retinal perivasculitis.* L *indicates lens.*

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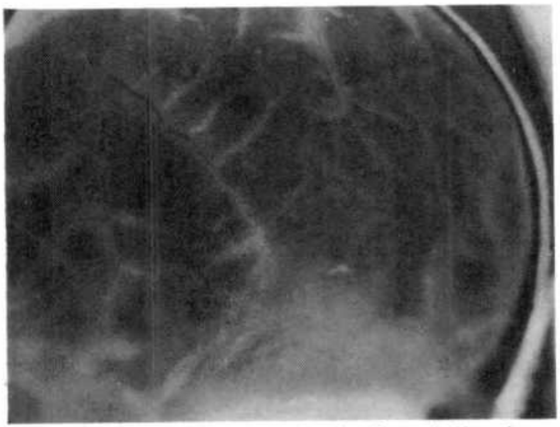

Fig. 2 *Dissecting micrograph of right calotte of affected globe showing retinal perivasculitis with extensive exudates and haemorrhages along inflamed vessels.*

view of the fundus. The eye was enucleated four days after the first signs of endophthalmitis.

The globe was bisected vertically through the optic nerve, some of the exudate in the vitreous collected, and a smear prepared and stained by Gram's method; the specimen was not cultured. The calottes were immersed in 2% paraformaldehyde and 2·5% glutaraldehyde in phosphate buffer, pH 7·4, for 24 hours and then studied under a dissecting microscope. With a blunt probe the opaque vitreous of the right calotte was separated from the retinal surface for better visualisation of the vitreoretinal border region (Fig. 1). Multiple posterior eye wall blocks were dissected out of the left calotte, dehydrated in graded concentrations of ethanol, embedded in paraffin, sectioned, stained with periodic acid Schiff and haematoxylin-eosin, and studied with a light microscope.

Results

Dissecting microscopy of the calottes revealed an opaque vitreous containing pockets of dense yellow exudate. Posterior vitreous detachment (PVD) was not present. The smear of the exudate showed Gram-positive cocci surrounded by large numbers of polymorphonuclear inflammatory cells. On separating the vitreous from the retinal surface in the right calotte (Fig. 1), a severe perivasculitis was revealed involving the arteries as well as the veins; multiple

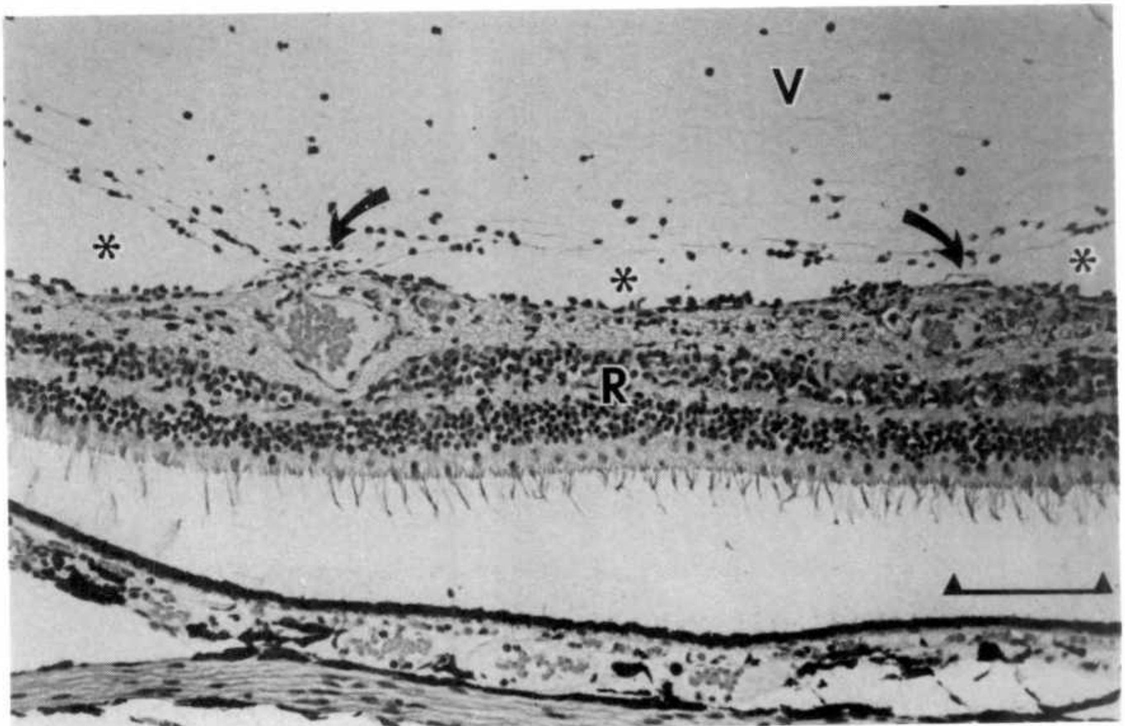

Fig. 3 *Light micrograph of vitreoretinal junction in left calotte of affected globe. Vitreous* (V) *is partially detached from retina* (R) *and is attached only along inflamed vessels (arrows). Vitreous, subhyaloid space (asterisks), and retina* (R) *show heavy infiltration by inflammatory cells. Retinal detachment is an artefact. Haematoxylin-eosin, bar=100 µm.*

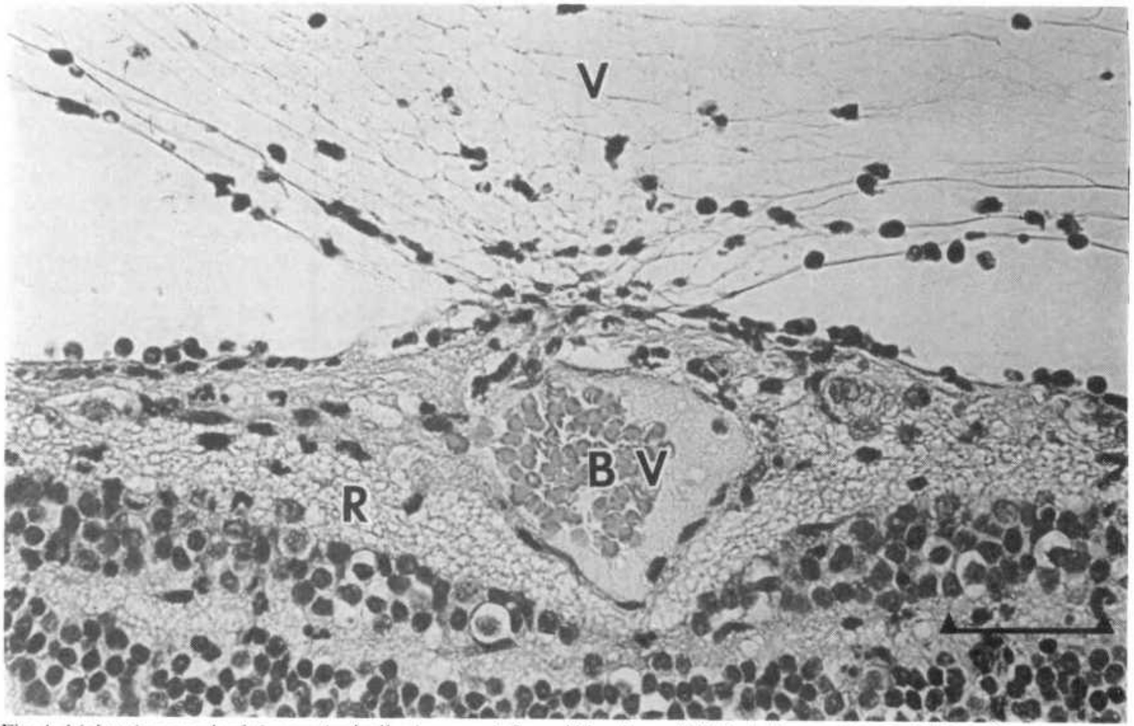

Fig. 4 *Light micrograph of vitreoretinal adhesion over inflamed blood vessel* (BV). *Adherent vitreous* (V) *is pulling on retina* (R). *Note polymorphonuclear inflammatory cells infiltrating vitreoretinal border structures and cuffing retinal blood vessels. Haematoxylin-eosin, bar=50* µm.

retinal haemorrhages were observed along the affected vessels (Fig. 2).

Light microscopy of the vitreoretinal junction in the left calotte (in which the vitreoretinal relationship was left undisturbed) showed strong adhesions of the vitreous cortex to the retina over the inflamed vessels (Fig. 3). The vitreous appeared to be in the process of separating from the retina; it was partly detached yet still adhering to and exerting tractional forces on the retina overlying the affected vessels. Numerous polymorphonuclear inflammatory cells were seen in the vitreous cortex and throughout the inner retina, particularly cuffing the blood vessels (Fig. 4).

Discussion

Examination of the primate eye demonstrated severe retinal perivasculitis and partial detachment (microscopic) of the posterior vitreous with strong vitreoretinal adhesions along the affected vessels. These findings were consistent in all the examined tissue blocks, so that an artefact can be excluded. As the injected gas leaked immediately from the eye, it could not have had any possible effect on the vitreous body.

Inflammation within the vitreous is known to produce opacification as well as liquefaction and shrinkage of this tissue,[6] with resulting PVD.[7,8] Endophthalmitis is also associated with retinal periphlebitis.[9]

Posterior vitreous detachment can produce retinal breaks if the outermost vitreous cortex adheres to the retinal surface.[10] Changes over vessels in the peripheral retina and subsequent pathological vitreoretinal attachments at these sites could explain some of the peripheral retinal holes caused by PVD,[11] while similar developments may lead to retinal breaks at the posterior retina.[12]

We suggest that a similar sequence of events may occur during the early stages of infectious endophthalmitis. PVD develops as a result of the inflammation and subsequent liquefaction and shrinkage of the vitreous body. This is turn induces tractional forces on the retina at the adhesion points along the inflamed vessels. It is possible that this traction may result ultimately in tractional or rhegmatogenous retinal detachment, but this still needs to be confirmed clinically.

Michels,[13] describing his technique for vitrectomy in endophthalmitis, states that no effort should be made to separate the posterior cortical vitreous from the retina if PVD is not present. His clinical impression is that in many eyes inflammatory debris causes adhesion of the posterior vitreous surface to the inner retina, and any attempt to separate the vitreous may result in tearing of the retina. Our findings support these clinical observations. Furthermore they suggest that the vitreoretinal adhesions may in fact occur in conjunction with the inflamed retinal vessels.

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The animal used in this study was maintained in animal care facilities fully accredited by the American Association of Laboratory Animal Science.

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Factors influencing visual outcome after cataract extraction among Arabs in Kuwait

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SUMMARY Of 409 consecutive Arab patients in Kuwait who had extractions for idiopathic (senile and presenile) cataract 385 were followed up for a minimum period of one year. Among these the final visual outcome was 6/12 or better in 208 eyes (54%) but visual acuity was 6/18 or less in 177 eyes (46%). Of these 177 eyes 127 eyes (71·8%) had poor vision due to preoperative ocular disorders and 31 (17·5%) due to surgical complications. The main ocular conditions which limited visual recovery were the presence of corneal opacities, hypermaturity of cataract, advanced glaucoma, senile macular degeneration, diabetic retinopathy, and postoperative retinal detachment in this order of frequency. The prevalence of these disorders in cataract patients among the Arab population was identified and is discussed.

The visual outcome and complication rate are the objective means of assessing the success of cataract surgery.[1 2] While modern cataract extraction is safe and effective, irreversible blindness either from the complications of advanced untreated cataract or from the complications of surgery may occur.[3] In addition associated ocular diseases increase the risk of complications and reduce the chances of a good visual outcome.[4]

The purpose of this article is to identify the main causes of poor visual achievement after cataract extractions in an Arab population in Kuwait, to highlight associated ocular problems with senile cataract, and to provide data about the prevalence of different eye disorders in this community.

Materials and methods

Four hundred and nine consecutive idiopathic (senile and presenile) cataract extractions in 352 patients were performed in the year 1983 at the Eye Department, Ibn Sina Hospital, Kuwait. Other types of secondary or traumatic cataracts were excluded.

A complete ophthalmic examination was carried out when each patient was admitted. Operations were performed by several surgeons with various levels of experience. There were 329 intracapsular cataract extractions (80·4%) and 80 (19·5%) extracapsular extractions in this series. Optical correction was achieved by aphakic spectacles in 97·8% of cases. Only 2·2% of cases had either soft contact lenses or intraocular lens implants.

Of the 409 eyes 385 (94·1%) had a satisfactory follow-up for a minimum period of one year. The best corrected visual acuity achieved after 12 to 18 months of follow-up was recorded, and a complete ophthalmic examination was conducted. The causes of visual acuity of 6/18 or less were determined where possible. The results were analysed and considered in relation to the prevalence of ocular disorders diagnosed preoperatively.

Results

Table 1 shows the age and sex distribution of 352 patients. Their ages varied from 34 to 95 years, mean 58·4. The male to female ratio was 1·3:1.

Table 1 *Age and sex distribution of 352 cataract patients*

Age groups	*Male*	*Female*	*Total*	*Percentage*
Under 40	9	7	16	4·5
40–49	41	19	60	17
50–59	72	56	128	36·4
60–69	48	45	93	26·4
70–79	22	24	46	13·1
80–89	4	3	7	2
90+	2	0	2	0·6
Total	198	154	352	100

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Table 2 *The visual acuities achieved after cataract extractions in 385 eyes*

Visual acuity	*n*	*Percentage*
6/12 or better	208	54·0
6/18–6/36	108	28·0
6/60–CF	60	15·6
HM–LP	6	1·5
No LP	3	0·8

CF=Counting fingers. HM=Hand movements.
LP=Light perception.

Table 2 shows the visual acuities achieved after 12 to 18 months of cataract extraction in 385 eyes. Of these, 208 eyes (54%) achieved a visual acuity of 6/12 or better and 177 eyes (46%) achieved 6/18 or less. Examination revealed that 127 out of 177 eyes (71·7%) had poor vision due to preoperative ocular disorders, and 31 eyes (15·8%) had poor vision due to surgical complications. There were 19 eyes (10·7%) that had visual failure due to multiple or undefined factors.

Table 3 shows the various preoperative ocular conditions which were responsible for poor visual achievement in 127 eyes. Corneal pathology, such as climatic droplet keratopathy (CDK) and trachomatous corneal scarring, represented 40·9% of cases. Optic nerve pathology was due to advanced glaucoma of a primary nature or lens induced. Macular and retinal diseases constituted 25·9% of cases. 66% of cases had 6/18 to 6/36 vision and 34% between 6/60 to fingers counting vision. There were no cases that had less than fingers counting vision in this group.

Table 3 *The associated ocular disorders responsible for visual acuity of 6/18 or less after cataract extraction*

Ocular disorder	*6/18–6/36*	*6/60–CF*	*HM–LP*	*No LP*	*Percentage*
Opaque cornea (trachoma+climatic droplet keratopathy +etc)	43	9			40·9
Lens induced glaucoma	9	13			17·3
Advanced primary glaucoma	5	10			11·8
Senile macular degeneration	10	4			11·0
Diabetic retinopathy	7	3			7·8
Retinal degeneration: (myopia+retinitis pigmentosa, etc)	7	2			7·1
Amblyopia	3				2·4
Optic atrophy (? aetiology)		2			1·8
Total (127 eyes)	84	43			100·1

Table 4 *The surgical complications responsible for visual acuity of 6/18 or less after cataract extractions*

Complication	*6/18–6/36*	*6/60–CF*	*HM–LP*	*No LP*	*Percentage*
Retinal detachment	3	3	2	2	32·3
Vitreous haemorrhage and opacities	2	4	2		25·8
After cataract	5				16
Cystoid macular oedema	1	2			9·7
Infection (endophthalmitis)			2	1	9·7
Decompensated corneas	2				6·4
Total (31 eyes)	13	9	6	3	

Table 4 shows long term surgical complications that resulted in a visual failure in 31 eyes. Of the 10 cases of retinal detachment (32·3% of cases) all had at least one operation for the condition, and retinal attachment was achieved in six eyes (60%). Organised vitreous heamorrhage due to combined surgical hyphaema and vitreous loss occured in five eyes, where blood entered the posterior segment from within the anterior compartment, and also opaque media after severe postoperative inflamatory reactions occurred in three other cases. Nine cases (29%) in this group (Table 4) had hand movements to no light perception.

Nineteen eyes with poor vision which could not be attributed to a main causative factor were found to have a combination of opaque cornea, raised intraocular pressure, and vitreous opacities.

Table 5 shows the prevalence of ocular disorders associated with senile cataract as diagnosed at the

Table 5 *The pre-existing ocular disorders associated with senile cataract in 385 eyes of Kuwaiti Arab patients*

Ocular disorder	*M*	*F*	*Total*	*Percentage*
Corneal pathology:				
Droplet keratopathy	33	13	46	11·9
Trachomatous corneal scarring	10	16	26	6·7
Non-specific corneal scarring	9	5	14	3·6
Cornea guttata	4	7	11	2·8
Complications of hypermaturity:				
Phacomorphic glaucoma	8	19	27	7·0
Phacolytic glaucoma	—	2	2	0·5
Subluxated lens	2	—	2	0·5
Glaucoma:				
Neglected closed angle	1	4	5	1·3
Chronic primary closed angle	1	2	3	0·8
Controlled open angle	3	2	5	1·3
Advanced open angle	1	2	3	0·8
Pseudoexfoliation	12	11	23	5·9
Strabismic amblyopia	2	1	3	0·8
High myopia	3	—	3	0·8
Diabetic retinopathy	4	2	6	1·6
Total	93	86	179	46·5

time of admission in 385 eyes, as well as the distribution of each disorder according to sex.

One hundred and seventy-nine eyes (46·5%) had some sort of ocular disorder when presenting for cataract extraction. In 97 eyes (25·2%) there were significant corneal opacities. Climatic droplet keratopathy represented 47·4% of corneal pathology and 11·9% prevalence among the cataract population in Kuwait; trachomatous corneal scarring represented 26·8% of total corneal pathology and 6·7% prevalence in the cataract population.

Hypermature cataractous lenses were present in 31 eyes (8%) when first seen. Twenty-nine of these patients presented because of ocular pain due to lens induced glaucoma. All cases had unilateral mature cataract in one eye and good visual acuity in the fellow eye. Lens induced glaucoma was more common in females, with a male to female ratio of 1:2.1.

Advanced glaucoma were found in 16 eyes (4·2%). There was equal prevalence of primary chronic closed angle glaucoma and simple open angle glaucoma. Chronic closed angle glaucoma showed a higher incidence in females, 6 out of 8 eyes (75%). Pseudoexfoliation was noted in 23 patients (5·9%) but was not associated with raised intraocular pressure.

Discussion

The visual outcome after cataract extraction in a selected series of patients with senile cataract was 6/12 or better in 81·6% of cases.[2] But the presence of identifiable eye disease besides the cataract increases the risk of operative complications and reduces the visual prognosis.[4] In a review of 500 cataract extractions by Chandler and Wadsworth[5] 5·4% of eyes had no improvement of vision owing to pre-existing ocular conditions such as macular changes, optic atrophy, or retinal detachment. The prevalence of senile macular degeneration in a cataract population was 13·2% in one study.[2] Further, the higher incidence of both cataract and macular degeneration in older people[6] makes the coexistence of the two conditions very likely. It has been found that the preoperative factor which mainly influences the outcome of cataract surgery is the presence or absence of macular disease.[7] While this holds true in developed countries, there are other limiting factors in developing communities that were not identified. In a study of 567 cataract extractions in Nigerians[8] the visual acuity achieved was recorded in only 49·2% of that series, and there was no mention of associated ocular disease.

Meredith and Maumenee classified cataract patients into three groups[4]: group 1, no preoperative factors predisposing to complication; group 2, visual improvement was hoped for, but not expected; and group 3, those eyes predisposed to operative or postoperative complications. The last two groups constituted 32·4% of eyes in their series,[4] but in our series 46·5% of the eyes fell in the last two groups.

If cases of opaque cornea and glaucoma were excluded from our series, 71·5% of cases would achieve 6/12 or better. Preoperative ocular diseases were found to be responsible for 77·1% of cases with visual failure after surgery in this series. Corneal opacities were the leading cause of poor visual outcome (41%). Trachomatous corneal opacities and climatic droplet keratopathy were found separately or more frequently combined. Climatic droplet keratopathy[9] is also known as Labrador keratopathy,[10] spheroidal degeneration of cornea,[11] and desert keratopathy in this part of the world. It is three times more frequent in males than females and also more severe. Because of its location in the central part of the cornea and the irregularity of the surface epithelium it frequently results in visual deterioration. Though vision is usually somewhat reduced (6/18–6/36), the disease occasionally produces profound visual failure, especially in association with trachomatous corneal scaring. Droplet keratopathy is related to ultraviolet radiation,[12] and females may be protected by wearing veils in this part of the world[13] or by being less exposed to sunlight, as they tend not to go outdoors as males do.

Though acute trachoma infections are infrequently seen among Kuwaitis now, the complications of healed trachoma are nevertheless commonly seen in older people. Cloudy to hazy corneas due to trachomatous corneal scarring, with variable degrees of dry eyes and eyelid malpositions, are daily seen in outpatient practice in the older population.

This situation necessitated a modification of preoperative and operative techniques. Patients frequently had lid surgery or rubbing lashes dealt with first. They might need frequent artificial tear drops before and after surgery. Fornix based conjunctival flaps became more popular, as it is easier to approach the limbus and avoid a scarred superior bulbar conjunctiva in limbal based flaps. Moreover the high incidence of opaque corneas and mature cataracts delayed the popularity of planned extracapsular cataract extraction techniques.

The second problem was the high incidence of lens induced glaucomas (phacomorphic and phacolytic). They were responsible for 17·3% of cases with visual failure after cataract surgery. In this group 21 out of 29 eyes (72·4%) failed to achieve good vision. Only eight eyes (27·5%) were able to achieve 6/12 or better. All the patients had good visual acuity in the fellow eyes. This observation may explain the delay in seeking medical help.

The third problem was neglected or inadequately treated glaucomas when patients did not seek proper medical care early enough or did not comply with the treatment. The visual achievement of those eyes was unsatisfactory on the whole (15 out of 16 eyes (93·7%) achieved 6/18 vision or less). Seven cases (43·7%) had combined glaucoma and cataract surgery.

Senile macular degeneration has a lower incidence among the cataract population in Kuwait (3·6%) than in Americans and Europeans[6,7] in the same age groups. Though senile macular degeneration was responsible for 11% of poor visual outcome after surgery, it was of mild degree. Ten out of 14 eyes (71%) had 6/18 to 6/36 vision. No cases with discform macular lesions were seen. All cases were of dry type.

Pseudoexfoliation was seen in 5·9% in this series in contrast to a higher incidence in Australian Aborigines[14] and a lower incidence in Americans.[15]

All amblyopic and strabismic eyes were identified preoperatively. Three out of 6 myopic eyes with myopic chorioretinal degeneration were identified, but none of the eyes with senile macular degeneration were suspected.

It is of interest to note that visual failure due to preoperative factors did not reduce visual acuity beyond fingers counting, but serious surgical complications did. Six of 31 eyes with surgical complications had hand movements to light perception and three eyes had no light perception.

The surgical complication rate for the whole series as regards retinal detachment (10 eyes), 2·6%, and endopththalmitis (three eyes) 0·7% correlates well with internationally reported figures.[4,16,17] Noteworthy is the higher incidence of cataract extraction in younger people (Table 1); 21·5% of patients were under 50 and 57·6% of patients were under 60. Such an observation needs further investigation in future studies.

Finally, we recommend earlier extraction of cataract to avoid the complication of hypermaturity, serious consideration of combined keratoplasty and cataract extraction when opaque cornea is thought to be a limiting factor for visual recovery, and the development of more experience in closed intraocular microsurgery (vitrectomy) to reduce the long term sequelae of surgical complications.

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Temporary corneal oedema after acute intake of alcohol

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SUMMARY A 65-year-old man had diffuse, bilateral corneal oedema after acute intake of alcohol. Three days later the total opacification began to clear from the peripheral area towards the centre of the cornea. One month later both corneas were completely clear, and visual acuity was 20/20 in both eyes. Specular microscopy showed in the right eye greatly enlarged endothelial cells, which subsequently shrank, and they showed some pleomorphism six months later. The pleomorphic endothelial cells in the left eye changed little with time. Our findings suggested that the corneal oedema in this patient resulted from temporary endothelial dysfunction with extensive cell loss.

It is well known that the acute intake of alcohol causes a disturbance of vision related to damage of the optic nerve.[1] To our knowledge no reports have described temporary corneal oedema from acute ingestion of alcohol. We describe such a case in a 65-year-old Japanese man.

Case report

A 65-year-old man drank about 1·0 l of distilled Japanese sake on 15 October 1984 and lost consciousness. The next day he was admitted to hospital for continued unconsciousness, dyspnoea, and cyanosis. Hypoglycaemia (16 mg/dl (0·89 mmol/l) and an elevated aspartate transaminase level (258 KU) were found. The results of the following tests were normal: renal function, haemogram, and blood ammonium concentration. No signs of infection were found.

On a diagnosis of hypoglycaemia-induced unconsciousness the patient was given an intravenous drip injection of glucose and oxygen inhalation. His blood glucose concentration increased to 104 mg/dl (5·8

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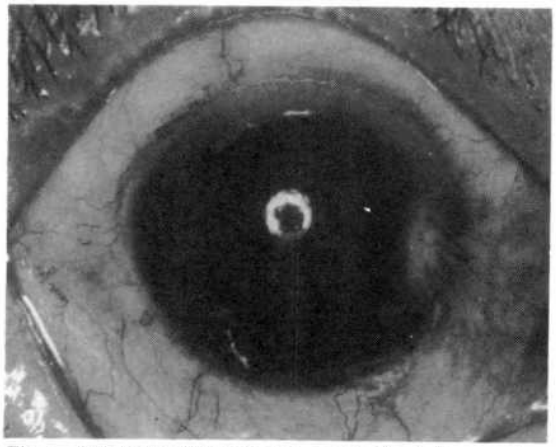

Fig. 1 *Corneal oedema was apparent in the right eye on the first hospital day.*

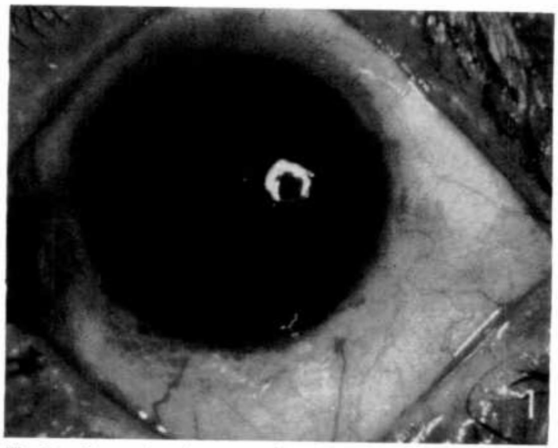

Fig. 2 *Corneal oedema was also observed in the left eye, though it was milder than in the right eye.*

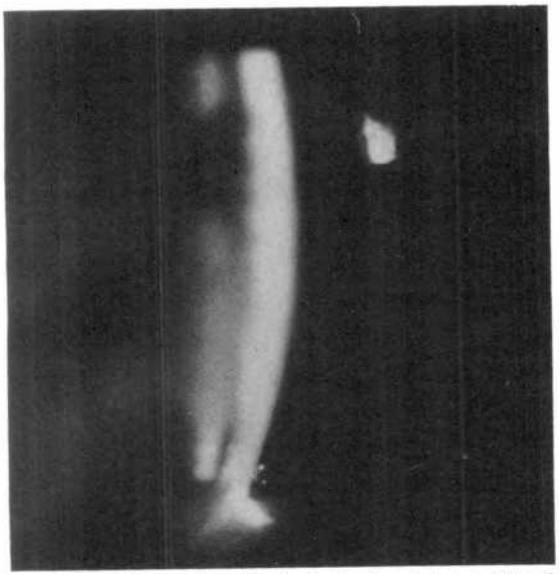

Fig. 3 *Total corneal opacity begins to clear in the peripheral area of the right cornea on the third day in hospital.*

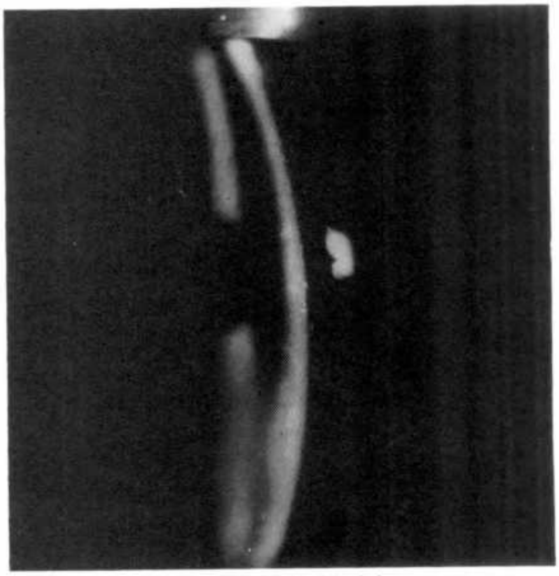

Fig. 4 *An area in the upper half of the left cornea starts to clear on the third day in hospital.*

mmol/l), he became conscious, and his cyanosis improved. On 17 October 1984 he noticed blurred vision in both eyes and was referred to our clinic. No lubricating drops had been applied nor had he used contact lenses. He had no history of ocular disease. Our examination showed a visual acuity of counting fingers OD and 10/200 OS, with best correction. Slit-lamp examination of the anterior segment disclosed bilateral corneal oedema (Figs. 1 and 2). Pachometry showed the corneas to be 0·73 mm thick in both eyes (about 1·5 times normal). Intraocular pressures were within normal limits. There were no abnormal findings in the lens, vitreous, or fundus in either eye.

On the diagnosis of idiopathic corneal oedema the patient was treated with vitamins A and B complex (B_1, B_6, B_{12}), and topical application of 0·1% dexamethasone and 0·05% vitamin B_2 eye drops three times a day. After three days the corneal oedema

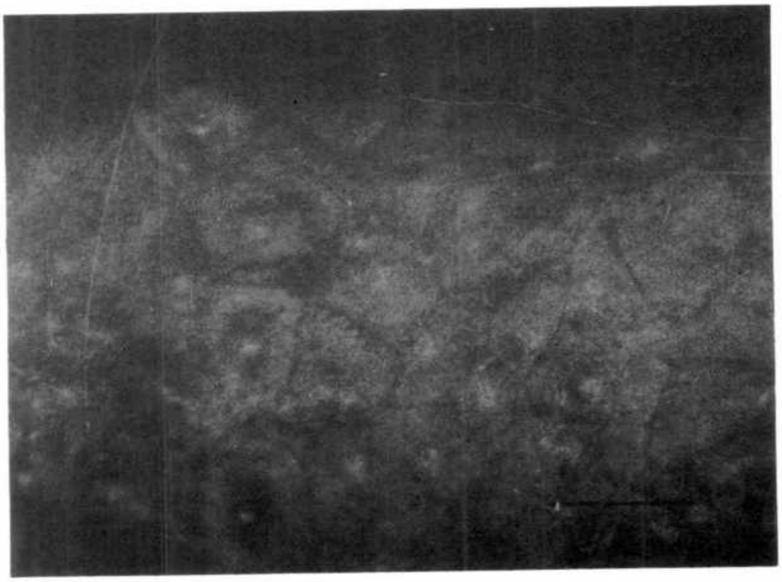

Fig. 5 *Extremely enlarged endothelial cells were found in the right eye. Bar=100 µm.*

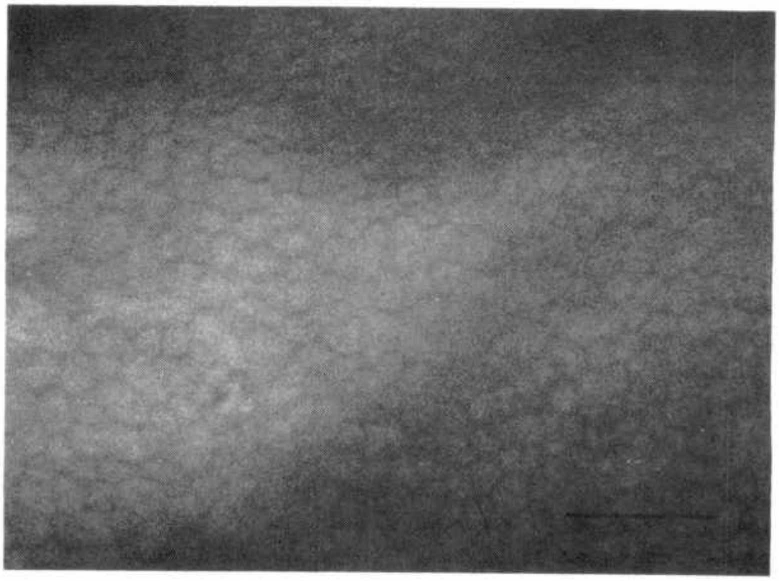

Fig. 6 *Pleomorphic endothelial cells were noted in the left eye. Bar=100* μ*m.*

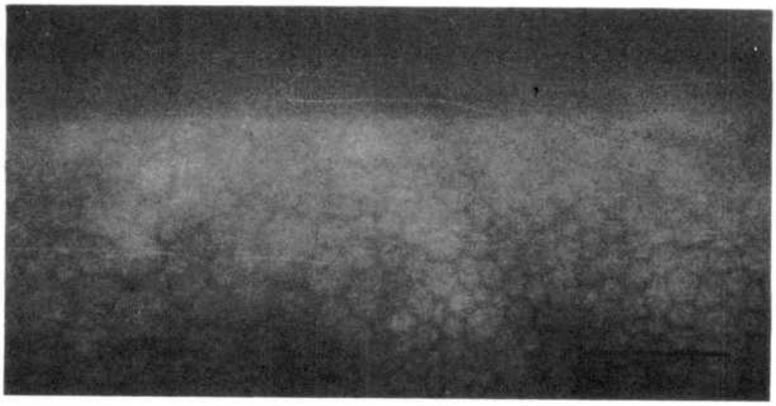

Fig. 7 *At six months greatly enlarged endothelial cells have shrunk, but some pleomorphic cells persist in the right eye. Bar=100* μ*m.*

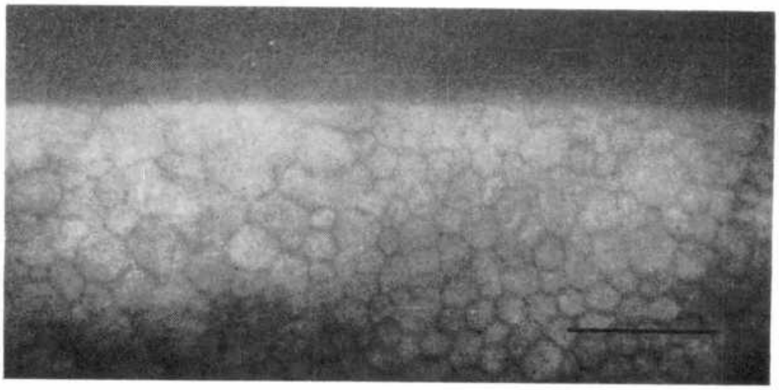

Fig. 8 *At six months pleomorphic endothelial cells are unchanged in the left eye. Bar=100* μ*m.*

began to decrease at the periphery (Figs. 3 and 4), the decrease continuing to the centre of the cornea. The right eye improved at a slower rate than the left. One month later both corneas were entirely clear, and visual acuity was 20/20 bilaterally.

Specular microscopy done on the fifth day after admission showed extremely enlarged endothelial cells in the right eye (Fig. 5) and pleomorphic endothelial cells in the left eye (Fig. 6). Specular microscopy repeated at six months showed that greatly enlarged cells in the right eye had mostly disappeared, though some large pleomorphic cells were noted (Fig. 7). The endothelial cells in the left eye remained pleomorphic (Fig. 8).

Discussion

Our patient had temporary corneal oedema after acute intake of alcohol. The initial specular microscopic observations showed extremely large endothelial cells in the right eye, which subsequently shrank, leaving some pleomorphic features; in the left eye pleomorphic endothelial cells remained unchanged with time. Interestingly, the peripheral area of the corneas started to clear first and the clearing then spread to the centre. These findings suggest that the transient corneal oedema in our patient was caused by temporary dysfunction of the corneal endothelium, with some loss of endothelial cells, particularly in the central area of the right eye. The difference in the severity of the cell damage between both eyes corresponded to the observed clinical course: the corneal oedema resolved in the left eye sooner than in the right eye.

It is unlikely that ethanol is directly toxic to the corneal endothelium, because similar reports of this condition are lacking in alcoholic patients. Moreover, no damage of the corneal endothelium was produced in experimental intraperitoneal injections of ethanol.[2] The prolonged hypoglycaemic condition of this patient may have been a factor in causing the oedema. His hypoglycaemia might have resulted in the very low aqueous glucose level, as the glucose concentration in aqueous humour[3] has been reported to be about 60% that of the glucose serum level. Because glucose has been reported as one of the important factors in the maintenance of the endothelial function of cornea[4] it is possible that the prolonged hypoglycaemia was a factor causing the corneal damage in this patient. It also seems possible that prolonged exposure of the eyes and hypoxia during his stupor were other factors that caused the corneal damage, though there may have been other unknown factors. Cyanosis was noticed in this patient and improved with oxygen inhalation. The combination of these factors may thus have caused the corneal damage.

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Epiretinal membranes in sickle cell disease

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SUMMARY Epiretinal membranes at the macula were seen in 4% of the eyes of 355 patients with homozygous sickle cell (SS) disease and sickle cell haemoglobin-C (SC) disease under the age of 60 years. The presence of proliferative sickle retinopathy (PSR), the extent of involvement of PSR, and vitreous haemorrhage all constitute risk factors for the formation of epiretinal membranes. The occlusion of PSR lesions by treatment appears to reduce the risk of epiretinal membranes being formed.

The vaso-occlusive process of sickle cell disease causes a wide variety of ocular disease. Attention has focused on proliferative sickle retinopathy (PSR), its natural history,[1-3] visual morbidity, and response of these lesions to therapy.[4] During ophthalmic assessment of Jamaican patients with sickle cell disease it became apparent that macular epiretinal membranes (ERM) developed. The characteristics of such membranes are presented in this report.

Materials and methods

The patients attended the sickle cell clinic at the University Hospital of the West Indies or a group of peripheral sickle cell clinics operated by the staff of the Medical Research Council (MRC) Laboratories. From 1 October 1983 to 1 October 1985 355 patients aged 15–60 years were examined for macular ERM. There were 132 patients with homozygous sickle cell (SS) disease and 223 with sickle cell-haemoglobin C (SC) disease (Table 1). Of this group 41 (12%) patients had been observed twice yearly for three years in an argon scatter study, 30 (8%) twice yearly in a xenon feeder vessel study,[4] and 284 (80%) annually for at least seven years. The average duration of observation was 6·4 years.

Patients with ERM were recalled for further investigation between 1 October 1985 and 1 January 1986. Assessment included ascertainment of visual symptoms and tests of corrected visual acuity, anterior segment, and intraocular pressure. Direct and indirect ophthalmoscopy were performed after mydriasis. Red-free and colour photographs were taken, and fluorescein angiography was performed where appropriate. The grading of ERMs proposed by Joondeph[5] was adopted and is illustrated in Figs. 1–4. Additional data recorded included the extent of PSR lesions (clock hours of retina involved), the type of therapy, the visual acuity and grade of ERM when first diagnosed and when last seen, the age and genotype of patients, and the duration of observation.

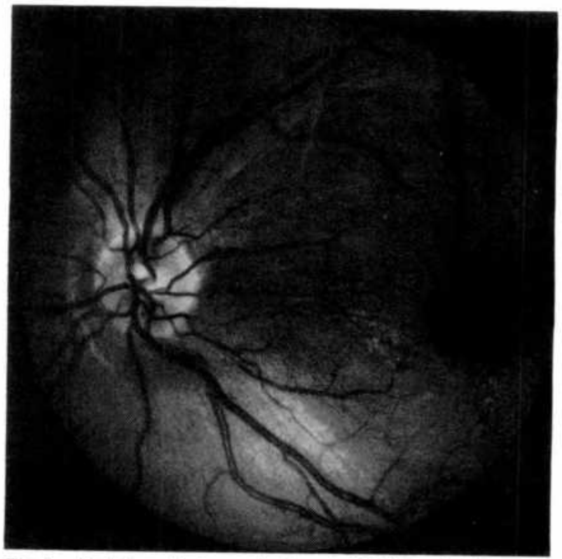

Fig. 1 *Red-free photograph of grade I ERM in the left eye of a 23-year-old male with SC disease. Note the altered light reflex, roughened appearance, but absence of retinal distortion.*

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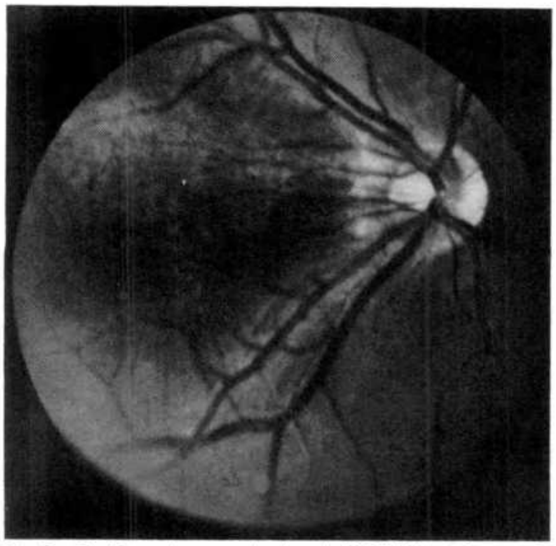

Fig. 2 *Red-free photograph of grade II ERM in right eye of a 25-year-old female with SC disease. There is a translucent membrane and some straightening of the papillomacular vessels.*

Certain groups were specifically excluded. Patients aged 60 years or over were excluded because of the difficulty in distinguishing age-related ERM in the normal population from those cases associated with sickle cell retinopathy. Eyes with proliferative vitreoretinopathy (PVR)[6] were excluded unless a preceding localised ERM had been documented. Eyes with macular wrinkling associated with vitreoretinal traction from elevated PSR lesions secondarily involving the posterior pole were excluded. Cataracts prevented assessments of the posterior pole in 11 eyes.

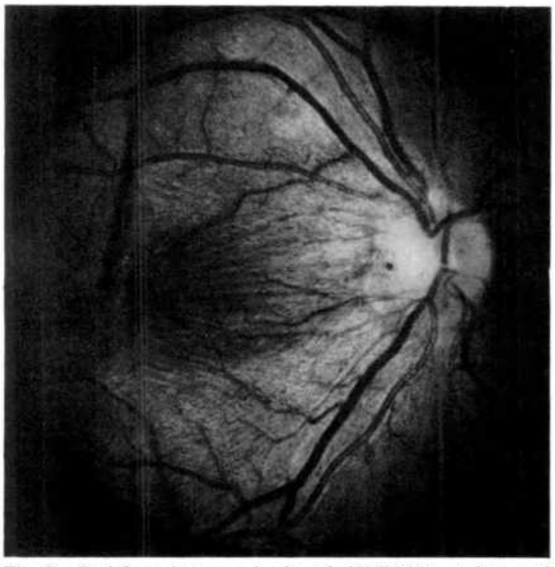

Fig. 3 *Red-free photograph of grade III ERM in right eye of a 29-year-old male with SS disease. There are striations of the retina and distortion and tortuosity of retinal vasculature.*

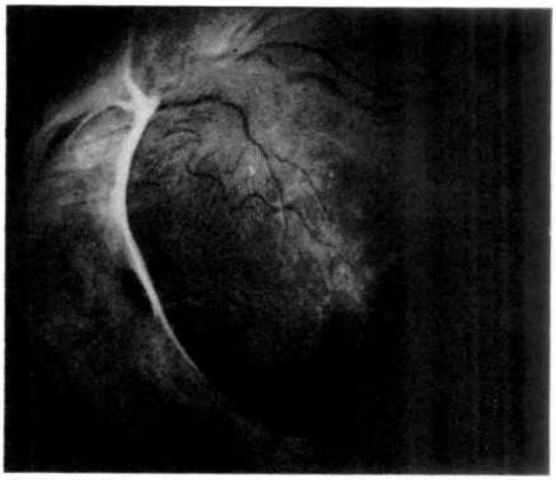

Fig. 4 *Red-free photograph of grade IV ERM in the left eye of a 20-year-old female with SC disease. There is a tractional detachment at the superotemporal arcade with a macular hole.*

Progression of ERM was deemed to have occurred with advance in grading of the ERM or if a fall in visual acuity of 2 lines or more was sustained on two occasions three months apart and this was not attributable to other pathology.

Results

Epiretinal membranes were observed in 25 eyes of 24 patients (Table 1) and were bilateral in a 42-year-old male with SS disease. The average age at diagnosis was 37 years (range 24–60 years).

All ERMs were associated with PSR in the same eye, the prevalence reaching 25/236 (11%) of eyes with PSR. They were significantly more common in the SC genotype, but this difference was accounted for entirely by the greater prevalence of PSR in SC disease.

Certain risk factors for ERM formation could be identified. Preliminary observations suggested that ERM formation was related to the extent of PSR, and this was tested by examining data from the 131 eyes admitted to the argon scatter and xenon feeder vessel trials. Within this group there was a highly significant association between ERM and extensive retinal involvement (>6 hours) by PSR (χ^2 for trend=21·7; $p<0·001$).

Vitreous haemorrhage also appeared to be a risk

Table 1 *Prevalence of epiretinal membranes according to sex and genotype in patients and in eyes examined*

	Male				*Female*				*Total*			
	Patients	*Eyes*	*ERMs*	*(% eyes)*	*Patients*	*Eyes*	*ERMs*	*(% eyes)*	*Patients*	*Eyes*	*ERMs*	*(% eyes)*
SS	54	107	3	(3)	78	154	0	(0)	132	261	3	(1)
SC	110	215	14	(7)	113	223	8	(4)	223	438	22	(5)
Total	164	322	17	(5)	191	377	8	(2)	355	699	25	(4)

factor for ERM formation, ERMs developing in 9/30 (30%) eyes with PSR and vitreous haemorrhage compared to 16/206 (8%) eyes with PSR but without vitreous haemorrhage ($\chi^2=11\cdot37$; $p<0\cdot001$). This relationship might be explicable by the association of vitreous haemorrhage with extensive PSR, which was highly significant in the subgroup of 131 eyes (χ^2 for trend$=27\cdot1$; $p<0\cdot001$) but even after this relationship was allowed for there remained a significant independent effect of vitreous haemorrhage (Mantel-Haenzel $\chi^2=4\cdot16$; $p=0\cdot04$).

The risk of developing an ERM appeared to be reduced by successful therapy of PSR lesions. Thus five patients with bilateral PSR developed ERMs in the untreated eye but never in the successfully treated eye. When analysed in the entire group, ERMs developed in 6% of treated eyes compared with 17% of untreated eyes ($\chi^2=6\cdot62$; $p<0\cdot01$) (Table 2). A similar difference persisted when the analysis was restricted to the eyes of SC patients ($\chi^2=6\cdot61$; $p<0\cdot01$). These data suggest that treatment inhibited the development of ERMs, but it is also possible that, if pre-existing ERMs had been considered a contraindication to therapy, such eyes would remain untreated and hence increase the apparent prevalence among untreated eyes. This hypothesis was tested by examining data from the 131 eyes enrolled in the photocoagulation trials, in which 75 were randomised to treatment and 56 to control groups. Subsequent observation indicated the development of ERMs in four unsuccessfully treated eyes (5% of treatment group) and in 10 untreated eyes (18% of controls), a significant difference ($\chi^2=4\cdot04$; $p=0\cdot04$).

Table 2 *Prevalence of epiretinal membranes in eyes according to genotype, sex, and treatment of proliferative sickle retinopathy*

	PSR untreated	*PSR treated*	*Total*
SS M	2/16 (12%)	1/13 (8%)	3/29 (10%)
F	0/9 (0%)	0/13 (0%)	0/22 (0%)
SS Overall	2/25 (8%)	1/26 (4%)	3/51 (6%)
SC M	10/44 (23%)	4/53 (8%)	14/97 (14%)
F	6/39 (15%)	2/49 (4%)	8/88 (9%)
SC Overall	16/83 (19%)	6/102 (6%)	22/185 (12%)
Total	18/108 (17%)	7/128 (6%)	25/236 (11%)

Visual acuity was reduced to 6/18 or less in 10/25 (40%) of ERM affected eyes and always attributable to the membrane. Acuity of 6/60 or less occurred in two (8%) eyes following traction detachment at sites of ERM formation.

Progression was observed in 8/25 (32%) of eyes with ERM during a mean observation period of 2½ years (range six months to seven years). A traction retinal detachment involved the macula in one patient with a fall in visual acuity to 6/24, but vitrectomy and membrane peeling allowed a retinal reattachment, and acuity was maintained at 6/12 nine months postoperatively.

Discussion

Epiretinal membranes were first described by Ivanoff in 1865.[7] Synonyms include Cellophane maculopathy, macular pucker, preretinal fibrosis, and surface wrinkling retinopathy. In a study of 1000 necropsy eyes there was pathological evidence of ERM in 5·4%, the prevalence increasing from 2% at age 50 to 20% at age 75.[8] The majority of ERMs are idiopathic and age-related, this group constituting 56% of the 328 eyes with ERM requiring surgery in a recent review.[9] Other causes in this study included postretinal detachment (29%), retinal vascular disease (4%), photocoagulation (3%), ocular inflammation (3%), trauma (2%), and vitreous haemorrhage (1%). The ophthalmoscopic features are elegantly described by Wise,[10] and treatment by vitrectomy and membrane peeling has yielded favourable results in many cases.[9 11-13]

The pathogenesis of ERM formation remains controversial. Simple idiopathic ERMs are thought to result from disruption of the internal limiting membrane by posterior vitreous detachment (PVD). This provides access for glial cells which migrate through breaks in that membrane and proliferate on the retinal surface,[14 15] providing a scaffold for fibroblastic elements.[16] The fibroblastic contractile membrane adherent to the internal limiting membrane causes secondary contraction of the superficial retina. The histopathological review by Clarkson *et* *al.*[17] confirmed that glial cells were the predominant cellular type and demonstrated continuity of the ERM with a site of disruption in the internal limiting membrane or with the optic nerve head.

Secondary ERMs are composed of glial cells, fibrocytes, macrophages, and retinal pigment epithelial cells in varying combinations. The fibrocytes and macrophages may be derived from retinal glial cells or from cortical vitreous cells (hyalocytes). Retinal pigment epithelial cells are the major type contributing to ERMs seen in rhegmatogenous retinal detachment.[14 17 18]

The present study indicates that sickle cell disease may also be a cause of ERMs. Risk factors for this complication include: (*a*) the presence of PSR; (*b*) extensive retinal involvement of PSR (>6 clock hours); (*c*) non-treatment or unsuccessful treatment of PSR; (*d*) pre-existing vitreous haemorrhage.

The common association of PSR with PVD may result in discontinuities of the internal limiting membrane and ingress of glial cells. Vitreous haemorrhage from PSRs may contribute by stimulating fibroplasia and activating cortical hyalocytes. Transudation of plasma from PSRs may disorganise the vitreous cortex further to increase the risk of posterior vitreous detachment. Dellaporta[19] suggested that subclinical, subretinal transudation into the macula from peripheral retinal lesions may contribute to ERMs.

There is insufficient evidence to explain why treatment of PSR reduces the risk of ERM formation. The occlusion of proliferative lesions decreases the risk of vitreous haemorrhage and transudation of plasma. This may decrease the incidence and progression of posterior vitreous detachment, the attendant disruption of the internal limiting membrane, and the subsequent ingress of glial cells.

The present study demonstrates a significant visual morbidity associated with ERM. The development of traction detachment in two eyes (8% of those with ERM) was caused by progression of localised ERM at the posterior pole and did not appear to be caused by traction from peripheral sites of vitreoretinal traction—the most frequent cause of traction detachment in proliferative sickle cell retinopathy.

Progression of ERM in sickle cell retinopathy resembles the unpredictable nature of idiopathic ERMs reported by Sidd *et al.*[20] They describe a case progressing from 6/7·5 to counting fingers in three months and other cases failing to progress after seven years. Spontaneous separation of ERMs was not observed in the present study but has been reported elsewhere.[21 22]

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Clearing media for the eye

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SUMMARY Non-ionic radiological contrast media have a high refractive index and are not toxic to living cells. They can be used as clearing media for unfixed ocular tissues. Corneal opacities in the rabbit could be made transparent, on a temporary basis, by soaking the stroma in contrast media, and no ill effects on the eye were noted.

It is an established technique to make tissues transparent by impregnating them with a solution of a high refractive index which matches that of the structural proteins and reduces their light scattering. In this way stereoscopic views of their internal structures can be obtained at a moderate magnification. This has required fixing the tissue, dehydrating it in alcohol, and soaking it in an organic solvent of high refractive index. Potts[1] established the optimal index to be 1·55 and recommended a mixture of methyl salicylate and oil of anise as being pleasanter to use than the more customary nitrobenzene. Water-soluble salts containing iodine can also achieve a sufficiently high refractive index, but the very high concentration of ions causes the collagen to shrink and the tissue to become distorted, as in the case of an ionised radiological contrast medium[2] or of potassium iodide.[3]

Recently non-ionised radiological contrast media have been introduced which contain a large proportion of iodine and accordingly have a high refractive index in solution. Two such, metrizamide (Amipaque*) and iohexol (Omnipaque*), are alcohols containing three iodine atoms per molecule. The potential of these solutions as clearing agents were examined in vivo as well as on isolated ocular tissues. Iohexol is supplied by the manufacturers in a sterile and stable solution at a concentration of 35 g/100 ml, while metrizamide can be made up to the same concentration from lyophilised powder that is readily available. The refractive index of these solutions is 1·46, and their tonicity was measured to be about twice that of tissue fluids.

Materials and methods

Ocular tissues, either fresh or fixed in formaldehyde and washed, were blotted dry and immersed in a small volume of the solution of contrast medium.

Central corneal leucomata were produced in albino rabbits while under ketamine general anaesthesia supplemented by topical proparacaine. Either about 10 µl of 1 N HCl was injected into the centre of the stroma or a small circle of filter paper soaked in 1 N NaOH was laid on the epithelial surface for a few seconds. In either case there was very little inflammatory response, but a central white scar was produced in the cornea which did not resolve in the succeeding days.

Treatment with the clearing agents was carried out on the animals similarly anaesthetised. If the epithelium had regrown after the chemical injury, it was scraped away from the central area with a scalpel blade. In some eyes the solution was applied in drops about every 30 s to the centre of the cornea, which was directed upward; in others a short plastic cylinder was pressed on to the eye round the limbus and sufficient solution was instilled into it to cover the apex of the cornea. When the treatment was prolonged for an hour, a cup filled with the solution was held over the cornea with a light suction.

Results

IN VITRO

Fixed human and fresh rabbit and beef tissues cleared very completely after about a half hour of soaking. Albino rabbit sclera became virtually invisible to the naked eye. Details of the vascularisation and pigmen-

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*Amipaque was supplied by Winthrop Laboratories, Sterling drug Co., New York, NY, and Omnipaque was a gift from Sterling-Winthrop Research Institute, Rensselaer, NY.

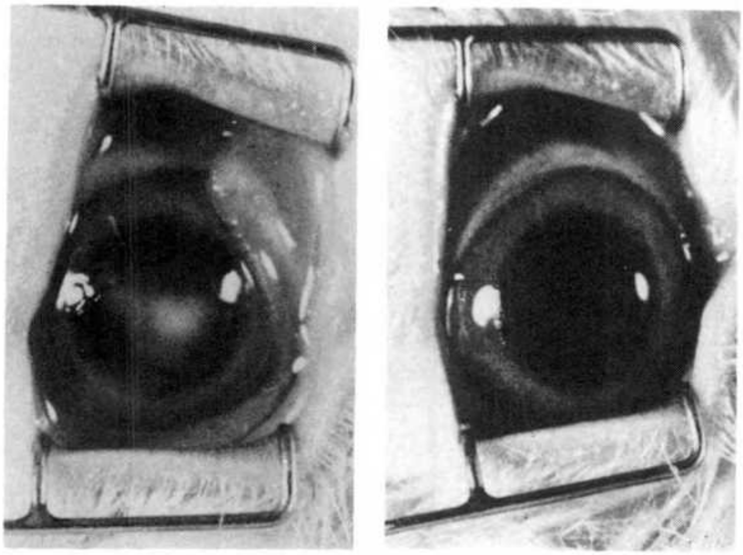

Fig. 1 Left: *Corneal scar created by caustic soda.* Right: *The same eye after removal of the epithelium and 20 minutes treatment with iohexol. The pupil was dilated to provide photographic contrast.*

tation can be observed under a dissecting microscope; the view was similar to that seen after treatment according to the method of Potts. Iohexol seemed slightly superior to metrizamide, but this was difficult to quantitate. The iris similarly cleared to allow satisfactory visualisation of its structure.

IN VIVO

In the eyes in which a large central corneal scar had been produced by acid or alkali no details of the retina could be seen with an indirect ophthalmoscope. Soon after treatment of the cornea with the medium it began to clear, and in about 20 minutes it became sufficiently transparent for full details of the fundus to be observed, as in a normal eye. The anterior segment could equally be examined with the slit-lamp through the cleared area. The stroma was seen to have thinned during the treatment. The scarred cornea remained fairly clear for 10 or 20 minutes after the treatment was stopped and then reverted to its previous state. (Fig. 1.)

Subconjunctival injections of about 50 μl of solution were made in albino rabbits, and the region of the ciliary body was examined in the slit-lamp to find out whether a better view of this structure and its circulation could be obtained. However, no substantial improvement was seen.

Similarly, in other eyes the aqueous humour was totally evacuated through a needle and then replaced with the clearing medium. This did not make a marked difference in the visibility of the structures and vessels of the iris.

TOXICITY

There was no permanent ill effects to the eye in these experiments, but a risk of injury to the tissues, particularly the corneal endothelium, is present, and further studies were made with greater exposure to the drugs.

Three normal corneas had their epithelium scraped off over a 6 mm diameter circle and were subjected to iohexol treatment for an hour rather than the 20 minutes needed to return clarity to the opaque cornea. The epithelium regrew without incident, and a few days later the only residual sign was a slight change in the refringence of the anterior stroma visible only in the slit-lamp. In two of the eyes the epithelium of the opposite eye was scraped off over the same area, but no treatment was given. The eyes were stained with fluorescein and observed under the slit-lamp daily thereafter. The epithelium regrew essentially at the same rate on both sides, the control eye being slightly advanced in one case and delayed in the other. The stroma was swollen in the bare area, as was to be expected, and was not substantially different on the two sides, as measured with an ultrasonic pachometer. This small difference does not suggest that any injury to the endothelium had occurred. Two eyes similarly treated for 1 h with metrizamide also recovered without incident and afterwards also showed a slight but rather great change in refringency of the anterior stroma.

In eyes where the aqueous humour was totally replaced with the clearing medium, two in each case, no signs of injury to the tissues and little inflammation was noted in spite of the high osmotic pressure of the solution and the absence of glucose and essential electrolytes. One day later the cornea had returned to its normal thickness, and two days later the needle track was the only sign of the intervention that could be noted with the slit-lamp or the naked eye, both the cornea and lens being indistinguishable from the control eye. Further testing did not seem warranted, since the threshold to injury for the human eye could be different from that of the rabbit.

The undiluted contrast media were also tested for their toxicity to primary or first-passage monolayers of tissue cultured rabbit corneal endothelium and keratocytes. The supernatant was sucked off and the cells were incubated under a thin layer of the contrast medium for various times before being covered again with tissue culture medium. It was found that both types of cells could withstand exposure to the contrast medium for up to 30 minutes without any morphological changes being noted at any time. After this they began to round up, and longer exposures led to detachment and apparent death for some of the cells.

Discussion

Non-ionic radiological contrast media are preferable to oils as a clearing medium for excised tissue samples. They have the advantage of simplicity and speed, and the treated tissue will remain in a more normal, possible viable, condition.

In the clinic it is possible that they will allow observation of the anterior chamber and the fundus in patients with scarred or oedematous corneas. It should also make it possible for these patients to estimate the benefit they might achieve from a corneal transplant. The barely detectable changes in the stroma would not be of importance in these cases, and from the few animal experiments it does not seem probable that injury to the epithelium or endothelium will occur; this needs to be tested in patients.

These media might have advantages over glycerol, which needs an intact epithelium in order to withdraw water osmotically from oedematous corneas and which can cause injury to the endothelial cells.[4] On the other hand their administration requires scraping away the epithelium from enough of the corneal surface to allow a view into or out of the eye, and this may be unacceptable as a procedure in many cases.

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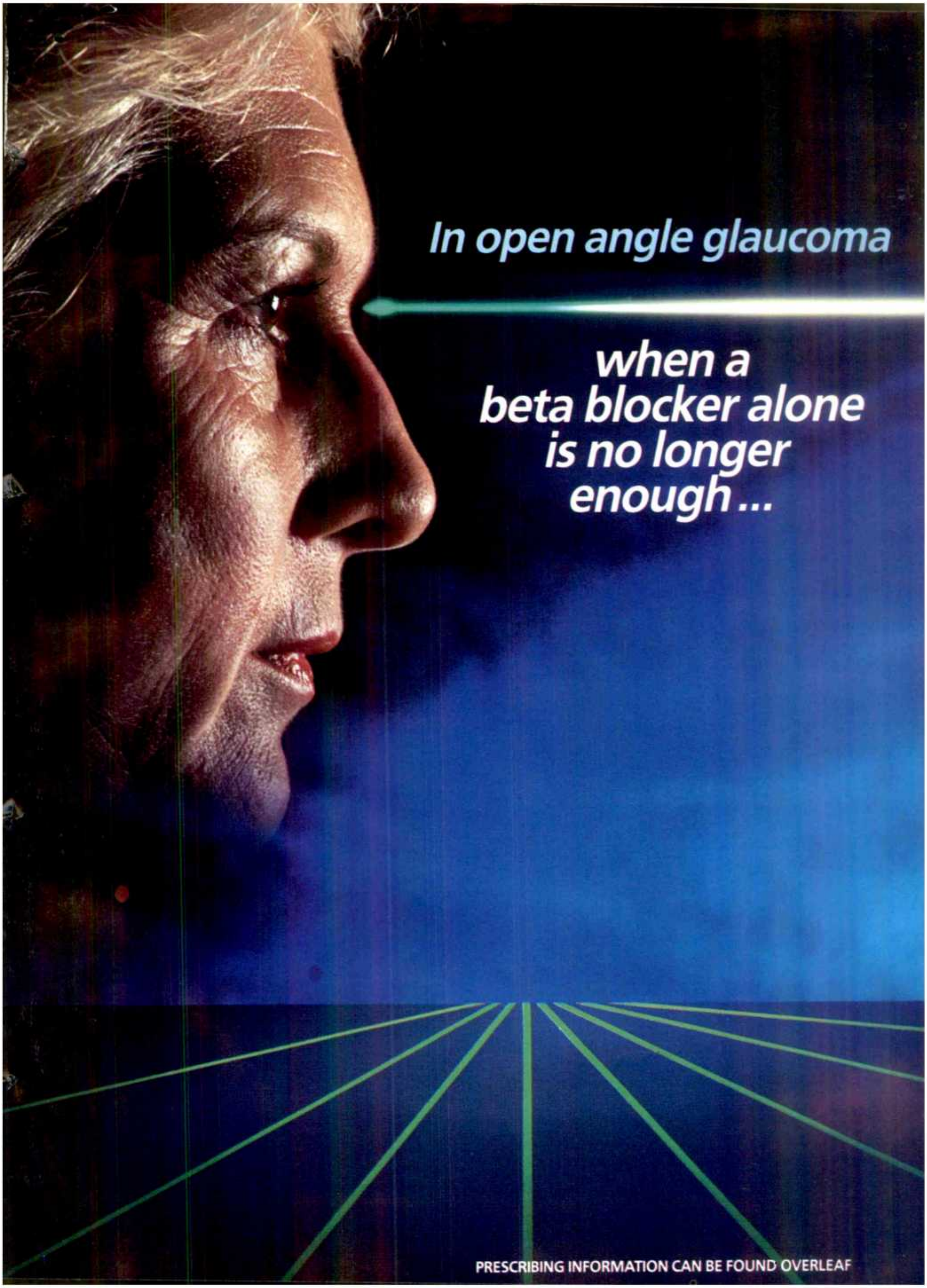
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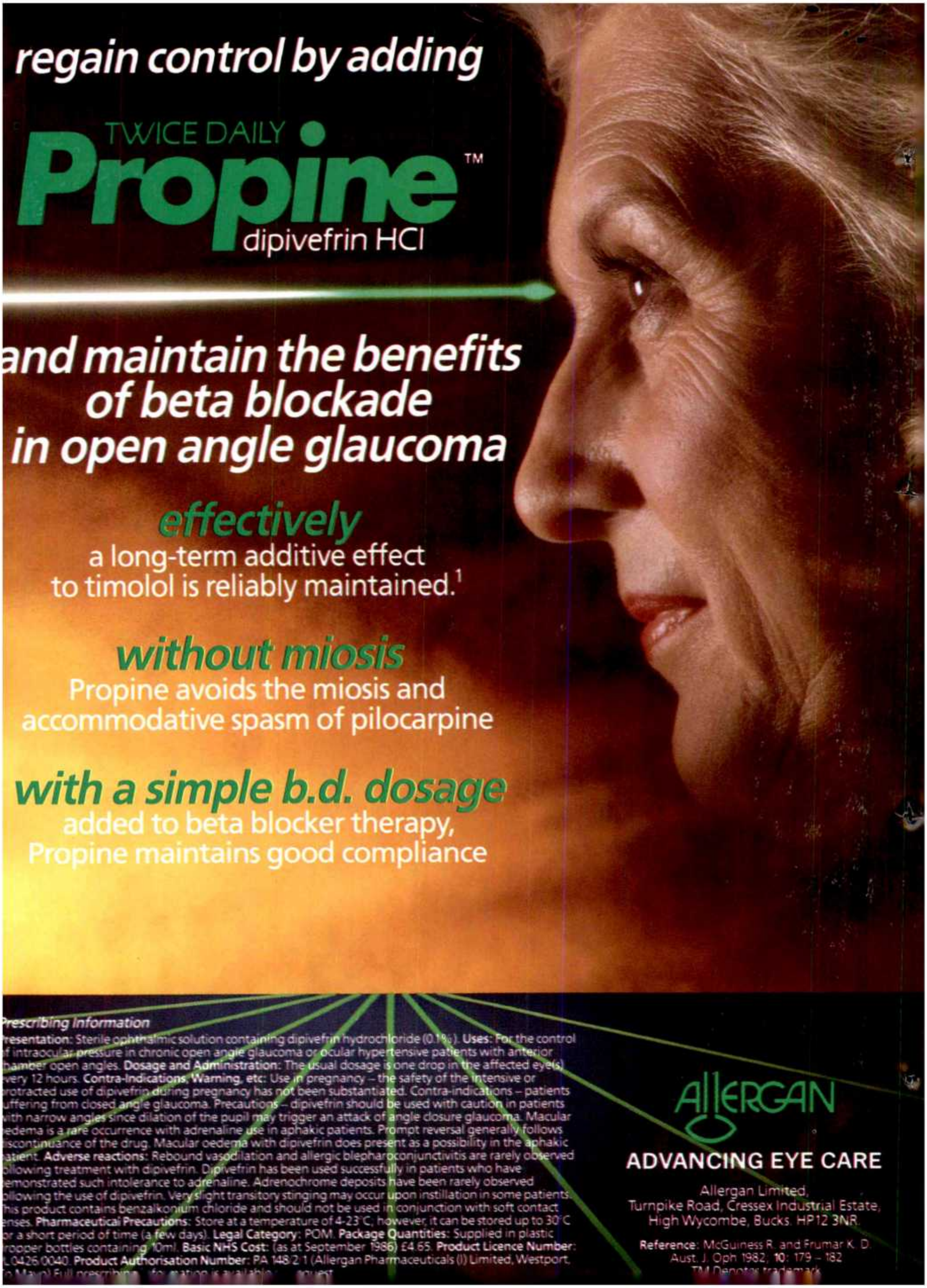

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British Journal of Ophthalmology, 1987, **71**, 473–476

Determination of the power of a convex-plano intraocular lens in situ from the dioptric keratometer reading of its front surface: extension table for the Javal-Schiøtz ophthalmometer

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SUMMARY The size of the reflex image of keratometer mires can be used to determine the power of an intraocular lens (IOL) inside the eye (in situ). The dioptric scale reading from the front surface of a convex-plano intraocular lens in cases of unknown power is compared with computed values. The accuracy of the method is demonstrated in a series of patients with known IOL power. Though in our study we have assumed convex-plano lenses are in use, the same procedure can sometimes be applied to lenses of different forms. To interpret scale readings below 30 dioptres and over 60 dioptres we compiled an extension table, suited to the ophthalmometer of Javal-Schiøtz (Haag-Streit), making use of low-powered minus and plus auxiliary lenses in front of the tube of the instrument.

Intraocular lens (IOL) power is controlled by the manufacturer to a high degree of accuracy before packing. Simple methods are available to the surgeon to check IOL power on the operating table before implantation.[1 2] Determination of the power of an IOL once it is inside the eye (in situ) may therefore seem to be a merely theoretical problem. However, there may be instances in which the determination of the power in situ acquires a practical interest—for example, when there is doubt about the IOL power used and other important data are lacking or are not reliable.

In our study we made use of the size of the reflex image produced by the front surface of a convex-plano IOL. Reflex images of the surfaces of an IOL are much clearer than the third and the fourth Purkinje images of the crystalline lens.

We used the ophthalmometer of Javal-Schiøtz (Haag-Streit) with a slightly increased target illumination by stronger bulbs. The instrument is built for the measurement of the reflex image of its mires produced by the surface of the cornea in air. But with the same instrument it is possible to observe the reflex image of the mires produced by the front surface of an IOL in situ. It should be understood, however, that the reflex image is observed through the magnifying system of cornea and aqueous. Neither the millimetre scale nor the dioptric scale of the instrument can directly be applied to the IOL. However, if we compare the dioptric scale reading from the front surface of a convex-plano IOL in situ with the values computed for variable IOL power in eyes with variable corneas and variable corneal vertex distances, this reading can be used to determine the power of the IOL. This method was presented for the first time at the first meeting of the European Intraocular Implantlens Council in 1982.[3]

Computation of the dioptric scale reading from the front surface of a convex-plano IOL in situ

Colenbrander[4] has demonstrated that the regression line for variations of the corneal refraction and the regression line for variations in depth of the anterior segment of the eye are for practical purposes straight lines. Therefore we selected as variables only three values (38, 43, and 48 dioptres) for the power of the cornea (F_c), three values (2·5, 3·5, and 4·5 mm) for the distance (d) between the apex of the cornea and the apex of the IOL, and five values (10, 15, 20, 25,

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and 30 dioptres) for the power of the IOL in situ (F_1).

There are thus three variables: F_c, d, and F_1. We executed a computation for the standard combination (F_c=43 D, d=3·5 mm, and F_1=20 D), and for the combinations of the above mentioned variations of only one variable in turn, combined with the standard values of the other two variables.

For these computations we made use of the principle of the 'equivalent mirror.' This principle states that a spherical surface (in this case the anterior surface of the IOL) seen through an optical system (in this case the cornea) is equivalent to a spherical surface in air, of which the position of the apex and the centre of curvature are the images formed by the cornea of the corresponding real points.

The computation and their results are shown in Appendix 1.

The results enable us to frame the following set of instructions.

Instructions for the determination of a convex-plano IOL in situ (refractive index 1·4917) having a refracting power within the eye between 10 and 30 dioptres

(1) Read with the ophthalmometer the dioptric value for the reflex image from the IOL inside the eye.

(2) Adjust this dioptric value to the corresponding value for the standard eye. This means: (*a*) if the dioptric power of the cornea is more (less) than 43 D, lower (raise) the dioptric value for the IOL by 0·53 D for each dioptre of difference; (*b*) if the depth of the anterior segment of the eye is more (less) than 3·5 mm, lower (raise) the dioptric value by 2·8 D for each mm of difference.

(3) Use Table 1 to convert the dioptric value in situ, adjusted for the standard eye, into the refracting power of the IOL.

Appendix 2 gives the comparison of the computed and the actual dioptric power of the IOL in a series of 11 patients.

Table 1 *Conversion of the dioptric reading with the ophthalmometer from a convex-plano IOL in the standard eye (cornea 43 D, anterior segment depth 3·5 mm) into the refracting power of the IOL in situ. I=Reading of the ophthalmometer in dioptres. II=Corresponding power of the IOL in situ, in dioptres.*

I	*II*	*I*	*II*	*I*	*II*
10	10·1	25	16·7	40	23·3
11	10·5	26	17·1	41	23·7
12	10·9	27	17·5	42	24·1
13	11·4	28	18·0	43	24·6
14	11·8	29	18·4	44	25·0
15	12·3	30	18·9	45	25·5
16	12·7	31	19·3	46	25·9
17	13·1	32	19·7	47	26·4
18	13·6	33	20·2	48	26·8
19	14·0	34	20·6	49	27·2
20	14·5	35	21·1	50	27·7
21	14·9	36	21·5	51	28·1
22	15·3	37	21·9	52	28·6
23	15·8	38	22·4	53	29·0
24	16·2	39	22·8	54	29·4
25	16·7	40	23·3	55	29·9

Extension table for the Javal-Schiøtz ophthalmometer (Haag-Streit)

The Javal-Schiøtz ophthalmometer (Haag-Streit) is calibrated to read the front curvature of the cornea from 30 dioptres to 60 dioptres. However, with the use of the ophthalmometer to determine the apparent curvature of the front surface of an intraocular lens inside the eye, dioptric values under 30 D and over 60 D may be encountered. Moreover, corneal curvatures under 30 D may occur in rare cases of cornea plana. On the other hand corneal curvatures over 60 D occur in cases of advanced keratoconus. Because the ophthalmometer scale does not allow the reading of these values, extension of the reading on both sides became necessary. We therefore developed an extension table for the Haag-Streit ophthalmometer, using a minus 2·5 D, a minus 1·25 D, or a plus 1·25 D auxiliary lens in front of the ophthalmometer tube. Stronger lenses cause difficulties with the forward and backward shift of the instrument.

An explanation of the method of computation is given in Appendix 3. The results are given in Table 2.

Table 2 *Conversion of scale readings with an auxiliary lens to the true values in dioptres*

With a minus 2·5 D auxiliary lens (conversion factor 0·5138)		*With a minus 1·25 D auxiliary lens (conversion factor 0·7416)*		*With a plus 1·25 D auxiliary lens (conversion factor 1·2855)*	
Reading	*True value*	*Reading*	*True value*	*Reading*	*True value*
30	15·4	30	22·2	45	57·8
31	15·9	31	23·0	46	59·1
32	16·4	32	23·7	47	60·4
33	17·0	33	24·5	48	61·7
34	17·5	34	25·2	49	63·0
35	18·0	35	26·0	50	64·3
36	18·5	36	26·7	51	65·6
37	19·0	37	27·4	52	66·8
38	19·5	38	28·2	53	68·1
39	20·0	39	28·9	54	69·4
40	20·6	40	29·7	55	70·7
41	21·1	41	30·4	56	72·0
42	21·6	42	31·1	57	73·3
43	22·1	43	31·9	58	74·6
44	22·6	44	32·6	59	75·8
45	23·1	45	33·4	60	77·1

Table 3 *Results of the computations on the various combinations of eye and IOL power*

	Data			*Results (F_o)*	*Diff.*
	F_c(D)	*d(mm)*	*F_l(D)*	*(D)*	*(D)*
Variation in F_c	38	3·5	20	35·26	0·53
	43	3·5	20	32·58	0·52
	48	3·5	20	29·97	
Variation in d	43	2·5	20	35·47	2·9
	43	3·5	20	32·58	2·8
	43	4·5	20	29·81	
Variation in F_l	43	3·5	10	9·88	2·27
	43	3·5	15	21·23	2·27
	43	3·5	20	32·58	2·27
	43	3·5	25	43·93	2·27
	43	3·5	30	55·28	

The last column shows that indeed the differences per unit are nearly constant. The values of 0·53 D per dioptre difference of F_c and of 2·8 D per mm difference of d are inserted in the instruction.
Results=readings on the ophthalmometer (F_o).
Diff.=difference per unit (D or mm).

Appendix 1. Computation of the dioptric scale reading from the front surface of a convex-plano IOL in situ

Here follows, as an example, the complete computation for the standard combination.

In order to be in accordance with dioptres, distances have to be measured in metres. However, we expressed distances in millimetres so as not to handle extremely small numbers, and in accordance multiplied the refractive indices by 1000.

The direction of the light rays is from within the eye to outside the eye. Distances behind the cornea are therefore negative.

I. First, we want to know the position of the image (d′) of the apex (d) of the IOL. The formula used is $A+F=A'$ or $(1000\,n/d)+F_c=(1000\,n'/d')$. $n=1·336$; $n'=1$; $F_c=43$ D; $d=-3·5$ mm. $(1336/-3·5)+43=(1000/-2·952)$. Thus $d'=-2·952$ mm.

II. Secondly, we want to know the radius (r_1) of the front surface of the IOL. The formula is $F_l=1000\Delta n/r_1$. $F_l=20$ D. $\Delta n=n'-n=1·4917-1·336=0·1557$. $20=155·7/7·785$. Thus $r_1=7·785$ mm, or in the computation $-7·785$.

III. The (real) position of the centre of curvature (c_1) of the anterior surface of the IOL is $c_1=d+r_1=-3·5-7·785=-11·285$ mm.

IV. Its image (c_1') is found along the same lines as in section I by the equation $(1000\,n/c_1)+F_c=(1000\,n'/c_1')$ or $(1336/-11·285)+43=(1000/-13·265)$. Thus $c_1=-13·265$ mm.

V. The radius of the equivalent mirror (r_e) is $-(c_1'-d')$ or $13·265-2·952=10·313$ mm.

VI. Just as with the cornea this corresponds with a power F_e. $F_e=(1000\Delta n)/r_e=(1336-1000)/10·313=32·58$. Thus $F_o=32·58$ D. This means that, if the ophthalmometer reading is 32·58 D, the IOL in the standard eye has a refracting power of 20 dioptres.

The same computations were made for the other combinations. The results are shown in Table 3.

Appendix 2 Comparison of the computed and the actual dioptric power in situ of the IOL in a series of 11 patients

F_c=Mean of the highest and the lowest reading (if there is corneal astigmatism) of the power of the cornea.
d=Distance from the apex of the cornea to the apex of the lens.
F_o=Reading on the ophthalmometer of the IOL in situ.
Corr. F_c=Correction for the variation of F_c.
Corr. d=Correction for the variation of d.
F_s=Adjusted reading for the standard eye.
F_l.I=Corresponding power of the IOL (D).
F_l.II=Actual power of the inserted IOL (D).

Patient no.	*F_c D*	*d mm*	*F_o D*	*Corr. F_c*	*Corr. d*	*F_s D*	*F_l.I D*	*F_l.II D*
1	43·75	3·5	26·6	− 0·4	+ 0·0	= 26·2	17·2	18·0
2	44·1	3·2	36·0	− 0·6	+ 0·8	= 36·2	21·6	21·0
3	45·0	3·3	35·1	− 1·1	+ 0·6	= 34·6	20·9	22·0
4	42·75	3·0	32·25	+ 0·1	+ 1·4	= 33·75	20·5	20·0
5	43·4	3·4	36·0	− 0·2	+ 0·3	= 36·1	21·5	21·5
6	44·5	3·4	24·75	− 0·8	+ 0·3	= 24·25	16·3	16·5
7	45·5	3·5	29·5	− 1·3	+ 0·0	= 28·2	18·1	19·5
8	47·5	3·4	31·0	− 2·4	+ 0·3	= 28·9	18·4	19·5
9	43·4	3·2	23·9	− 0·2	+ 0·8	= 24·5	16·4	16·0
10	43·0	2·7	33·75	− 0·0	+ 2·2	= 35·95	21·5	19·5
11	44·75	3·15	31·25	− 1·0	+ 1·0	= 31·25	19·4	19·5

Appendix 3 Computations for the extension table for the Haag-Streit ophthalmometer

The distance from the plane of focus of the Haag-Streit instrument to the front of the tube for an emmetropic observer and the eyepiece in the emmetropic position is 126 mm. The distance from the focal plane to the auxiliary lens is therefore 125 mm. The divergence of the lightrays coming from the focal plane at this position is exactly 8 dioptres. This is the divergence that the instrument requires at this spot in all circumstances.

A lens of +1·25 dioptres needs a divergence of 9·25 dioptres on entering the lens in order to obtain the divergence of eight dioptres when leaving the lens. The focal plane is then at 1/9·25 D=108·11 mm distance and the shift is 16·89 mm forward.

In the same way the distance to the focal plane with a −1·25 lens will be 1/6·75 dioptres=148·15 mm and the shift 23·15 mm backward.

With the forward shift and backward shift of the instrument in the reading position known, its influence on the size of the reflex images, and thus on the dioptric scale of the ophthalmometer, can be calculated. This influence is twofold: (*a*) a change of the angle with which the ophthalmometer mires present themselves to the patient's eye; and (*b*) a change of the observation angle of the reflex images. Both aspects can be expressed in terms of magnification, and thus the final magnification can be calculated.

In an ophthalmometer the coloured objects and the tube are linked together. They go both to and fro. But suppose for a moment that they were not linked. Then it would be possible to move only the objects forwards, which gives a real magnification of the reflex images, and see them in the normal way. Or it would be possible to move only the tube with the plus lens forwards. Then we should have reflex images of normal size, seen enlarged. However, if both the objects and the tube are shifted forwards, there must be a twofold magnification. Each of these magnifications is equal to the proportion of the distances to the focal plane without and with the additional lens. The normal distance from the coloured objects to the focal plane is 168 mm. Thus the magnification with the plus 1·25 D lens is:

for the shift of the coloured objects $M_1=\dfrac{168}{168-16·89}=1·112$,

and for the tube $M_2=\dfrac{125}{125-16·89}=\dfrac{9·25}{8}=1·156$,

and for both $M_1\times M_2=1·112\times 1·156=1·2855$. The magnification with the minus 1·25 dioptre lens is:

for the shift of the coloured objects $M_3=\dfrac{168}{168+23·15}=0·879$, and for the tube $M_4=\frac{125}{125+23\cdot15}=\frac{6\cdot75}{8}=0\cdot844$,

and for both $M_3\times M_4=0\cdot879\times0\cdot844=0\cdot7416$.

In the same way the magnification with a −2·5 D lens is $0\cdot7473\times0\cdot6875=0\cdot5138$.

These magnification factors are applicable only to the Haag-Streit keratometer and not to other instruments. However, the same method could be applied to other makes, if the relevant dimensions were measured or obtained from the manufacturers. The results of this computation are shown in Table 2.

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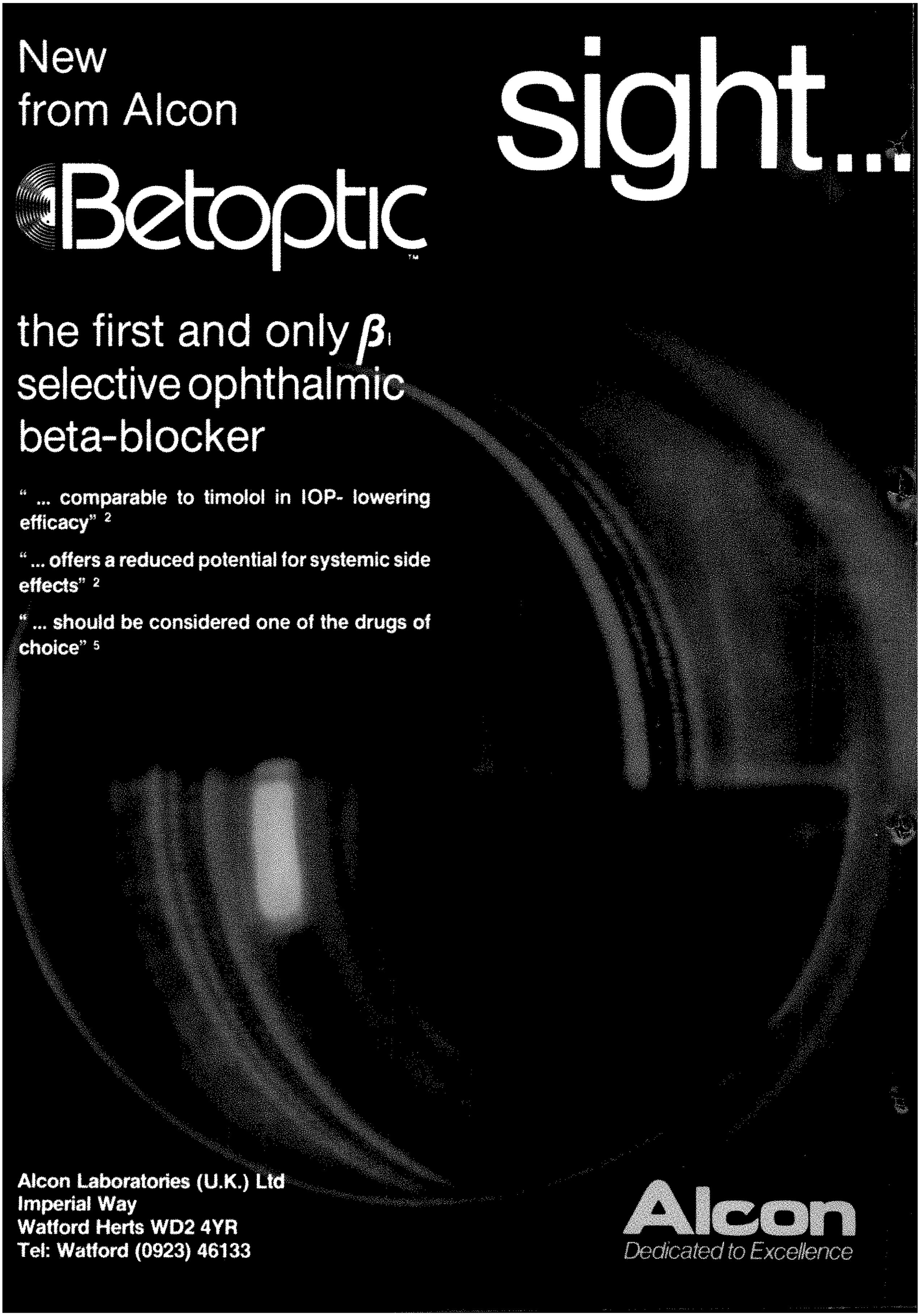

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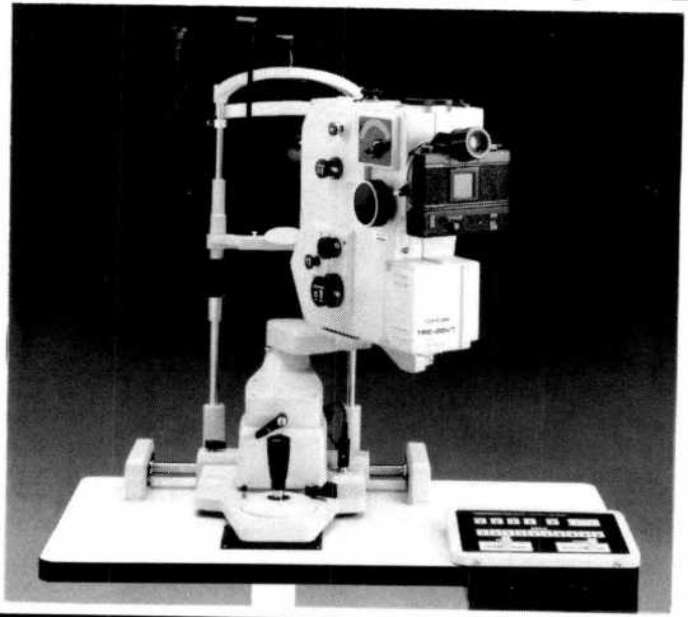

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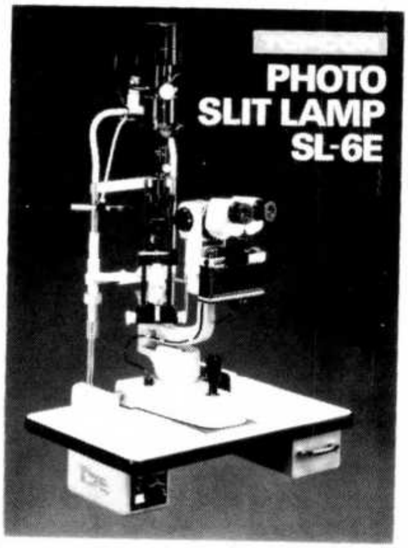

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Changes of MK medium during storage of human cornea

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SUMMARY By comparing the composition of McCarey-Kaufman (MK) medium before and after corneal storage we attempted to identify specific physiological changes in the medium as predictors of tissue damage. We also tried to determine if hydrocortisone (a lysosomal membrane stabiliser) added to the medium could reduce tissue damage during storage. Corneas (human and rabbit) were stored in the MK medium with and without hydrocortisone for 4 days at 4°C. The water and nitrogen contents of the stored cornea were compared with those of the fresh cornea. The medium was analysed before and after corneal storage to determine the concentrations of glucose, protein, and amino acids as well as pH and osmolarity. Scanning electron microscopy (SEM) was used to estimate the degree of the corneal endothelial cell damage. The nitrogen contents and dry weights of the steroid treated and untreated stored corneas were similar to those of the fresh unstored cornea. The steroid treated cornea contained a lesser amount of water than the untreated cornea. The cornea stored in medium without steroid took up a greater amount of glucose from the medium than the cornea stored in medium with steroid. As compared with their concentrations in the fresh unused medium the concentrations of leucine, lysine, and glycine were lower and that of glutamic acid was higher in both the media used for corneal storage. However, the steroid treated storage medium as compared with the untreated storage medium had a greater reduction in the lowering of leucine, lysine, and glycine, and a lesser reduction in the increase of glutamic acid. Steroid treated medium also had a lesser amount of protein released from the stored cornea. Changes in the pH and osmolarity of the media before and after corneal storage were not remarkable. SEM showed that the endothelial cells of the cornea stored in the medium containing steroid were less damaged than those of the cornea stored in the medium without steroid.

An alteration of the chemical composition of the aqueous humour of donor eyes stored in the moist chamber can adversely affect the corneal endothelium.[1] From this we speculated that if the tissue culture medium (McCarey-Kaufman (MK) medium) containing a stored cornea is not replenished, its chemical composition would change by the tissue products and that the change in the composition of the medium might cause adverse effects on the endothelium of the stored cornea. In this experiment we studied the nature of the biochemical alteration of the storage medium. We also tried to see if the addition of steroid[2-5] in the medium would influence the alteration of the chemistry of the medium. We analysed the storage medium for the absence or reduction (due to the influx or entrance into the stored cornea) and presence or increase (due to the efflux or exit from the stored cornea) of certain specific biochemical substances in the medium. As our previous works[2-5] showed that steroids can retard corneal autolysis, we studied the effect of hydrocortisone on the entrance and exit of these specific substances into and from the stored tissue.

Methods and materials

Full-thickness human and rabbit corneas were stored in the MK medium in the presence and absence of hydrocortisone (hydrocortisone 21 sodium succinate, Sigma Chemical, St Louis, Mo) at 4°C for 4 days. The medium actually used for corneal storage was called

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the 'used' medium in contrast to the 'unused' medium (fresh medium), which did not at any time come in contact with the tissue. The used medium was of two kinds: (*a*) experimental medium which contained the steroid, and (*b*) control medium which did not contain it. The particular storage time was chosen because it was observed previously by Liao *et al.*[5] that about this time a moderate amount of cellular damage occurs in the cornea stored in tissue culture media. After this time the compositions of the experimental and the control media were analysed. The fresh medium was also simultaneously analysed. A comparison of the three types of media (experimental, control, and fresh) was then done in terms of their glucose, protein, and amino acid contents as well as their pH and osmolarity.

All biochemical data were expressed with reference to a given diameter (11 mm) of the full-thickness cornea or in terms of a given amount of corneal nitrogen.

HUMAN CORNEA

Eye bank eyes received within 12 hours of death were used. A pair of human donor eyes (n=10 pairs) were sterilised by the usual eye bank procedures, and the corneas with a thin scleral rim (about 1 mm) were excised. One of the pair of corneas was placed in the experimental medium (20 ml) containing 10^{-6}M hydrocortisone and the other cornea in the same quantity of the control medium.

RABBIT CORNEA

As human corneas were not available in a fresh state (i.e., immediately after the donors' death), in order to study the effect of storage on corneas having a minimal post-mortem autolytic change, corneas of rabbits soon after their death (fresh cornea) were used. Healthy albino rabbits (3–4 kg) were killed with an overdose of sodium pentobarbital (Nembutal, Abbott Laboratories, Montreal). Both eyes of a rabbit were immediately enucleated and sterilised by the usual eye bank procedure. The corneas (n=10 pairs) with a thin scleral rim (about 1 mm) were excised and stored in the experimental and control media as done in the case of the human corneas. Additional fresh rabbit corneas (n=4) were also analysed for their water and nitrogen contents.

TECHNIQUES USED ON THE CORNEA

(*a*) *Measurement of dry weight*. Each sample of the cornea with a rim of sclera (corneal sample) was rinsed in cold saline and transferred into a preweighed test tube. The tube was kept in a desiccator at 60°C for 18 hours, and then reweighed with a Mettler H18 balance (Fisher Scientific Co., Don Mills, Ontario). The difference in weights was the dry weight of the corneal sample.

In order to estimate the dry weight of the cornea proper (i.e., without the scleral rim), a number of full-thickness trephined discs, 11 mm in diameter (corneal disc) were obtained from freshly enucleated rabbit eyes as well as from human donor eyes. The dry weights of the corneal discs were determined by the technique mentioned above.

(*b*) *Determination of total nitrogen*. Each of the dried corneal samples and corneal discs were treated with 0·5 ml of a mixture containing sulphuric acid in a saturated solution of copper sulphate. After the completion of digestion the amount of nitrogen in the given amount of tissue was estimated by the micro-Kjeldahl technique.[6]

(*c*) *Scanning electron microscopy (SEM)*. Corneal samples were fixed in the universal fixative (1% glutaraldehyde and 4% formalin in phosphate buffer, pH 7·2) at 4°C for 24 hours.[2] The tissue was washed several times with phosphate buffer (pH 7·2), and was postfixed in 1% buffered osmium for one hour at room temperature. The tissue was dehydrated in ethanol and dried by the carbon dioxide critical point method. The cornea was mounted with the endothelial side up on a stub and sputter—coated with gold. The specimen was examined by a scanning electron microscope (S-180-SEM Cambridge, England). From the photomicrographs the ratio of the damaged and undamaged cells was calculated.

TECHNIQUES USED ON THE MEDIA

(*a*) *Determination of glucose*. The glucose concentration of the MK media was determined using O-toluidine reagent (*Sigma Technical Bulletin* 635, Sigma Chemical Co., St Louis, Mo). Each sample of the medium was centrifuged at 2000 rpm for 5 minutes (Sorvall, GLC-1 Newton, CT). The absorbance of the supernatant was measured at 635 nm with a spectrophotometer (Beckman DU 2400, Beckman Instrument Inc, Fullerton, CA). Standard glucose solutions were used as reference.

(*b*) *Measurement of protein*. The protein content of the MK media was determined by two methods—UV wavelength method Whitaker and Granum[7] and Lowry and colleagues' method.[8] Bovine serum albumin was used as the reference standard in both instances.

(*c*) *Amino acid analysis*. Amino acid concentrations of the media were determined both before and after hydrolysis of the samples. Hydrolysis was done to break down proteins coming out from the stored cornea into amino acids.

With respect to the unhydrolysed sample, 50-µl aliquots of the medium were assayed with an amino acid analyser (Beckman model 12/M, Palo Alto,

Table 1 *Analysis of human and rabbit full-thickness corneal discs*

	Human				*Rabbit*			
	Stored in medium		*Unstored*	*Significance of difference (p)*	*Stored in medium*		*Unstored*	*Significance of difference (p)*
	With steroid (A)	*Without steroid (B)*	*Fresh (C)*	*(B–A)*	*With steroid (A)*	*Without steroid (B)*	*Fresh (C)*	*(B–A)*
Dry weight (mg)	24·94±0·01	25·12±0·04	24·94±1·07	<0·2	16·70±0·90	18·47±1·90	16·30±1·38	<0·2
Nitrogen content (mg)	2·96±0·17	3·06±0·01	2·91±0·50	<0·5	2·0±0·5	2·11±0·10	2·10±0·11	<0·5
Water content (mg)	107±7·00	122±6·00	108·57±5·20	<0·05	68·60±8·00	86·80±2·00	62·90±4·00	<0·01

California). With reference to the hydrolysed medium, 1 ml aliquots of the medium were transferred into a hydrolysing tube and lyophilysed overnight. For hydrolysis 0·5 ml of 6 N HCl was added into the tube, sealed under vacuum, and heated at 100°C overnight. The hydrolysate (50 µl aliquots) was then assayed with the analyser. Appropriate amino acid solutions were used as the reference standards. The amino acid analysis was done by the Amino Acid Analysing Service, Medical Sciences Building, University of Toronto, Toronto, Canada.

(d) Measurement of osmolarity. Standard filter paper discs were saturated with the medium and the osmolarity measured with a vapour pressure osmometer (Model 5100 B Wescor, Inc., Logan, Utah). Standard mmol/kg solutions were used as reference.

(e) Measurement of pH. The pH of the medium was determined with a pH meter (Beckman Zeromatic SS 3, Beckman Instruments Inc., Fullerton, Ca).

STATISTICAL ANALYSIS

The difference between the amount of a given substance in the fresh medium and the amount of the same substance in the experimental or control medium was determined. The difference in the amount of a target agent in the fresh cornea and the amount of the same substance in the stored cornea was also determined. The significance of the difference of the values in each case was analysed by means of the Student's *t* test and/or Wilcoxon sign rank test.

Results

Corneal analysis. As shown in Table 1, in the dry weight and nitrogen content there was no significant difference between the steroid treated and untreated stored corneas, nor was there any difference between either of these and the fresh corneas. However, the water content of the cornea stored in the experimental medium was significantly lower than that of the cornea stored in the control medium. Water content of the fresh cornea was lower than that of the corneas stored in the control medium, but it was similar to that in the experimental cornea.

Media analysis. The results related to the human cornea are given in Figs. 1 and 2, and that related to

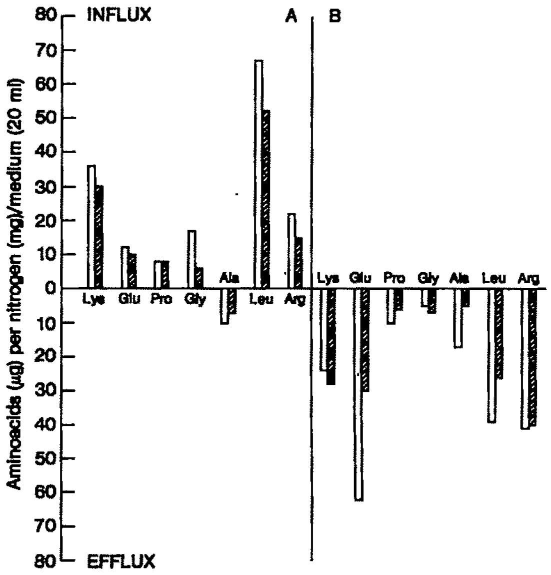

Fig. 1 *Amino acids in medium with hydrocortisone (striped bar) and without hydrocortisone (open bar) used to store human cornea, A, unhydrolysed medium, B, hydrolysed medium. The line at the 0 mark represents the values of unstored fresh medium. The values above the line indicate the loss of a given amino acid from the media (i.e., influx into the cornea. The values below the line indicate the gain of a given amino acid into the medium (i.e., efflux from the cornea)).*

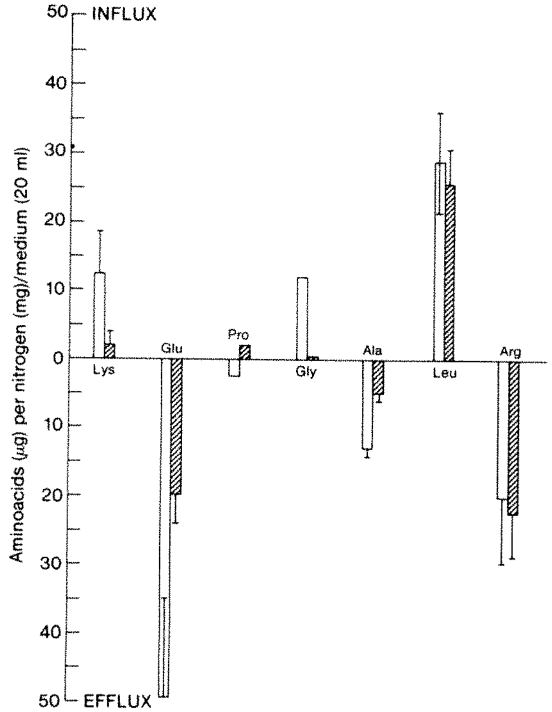

Fig. 2 *Net efflux and influx of amino acids in medium with hydrocortisone (striped bar) and without hydrocortisone (open bar) used to store human cornea. Standard error of mean is shown.*

the rabbit cornea in Fig. 3. Any increase or decrease of a given substance in the experimental and control medium above or below the quantity of the substance present in the fresh medium has been considered to have resulted respectively from a leaching out of the substance (efflux) from the stored cornea or an entrance of the substance (influx) into the cornea from the medium.

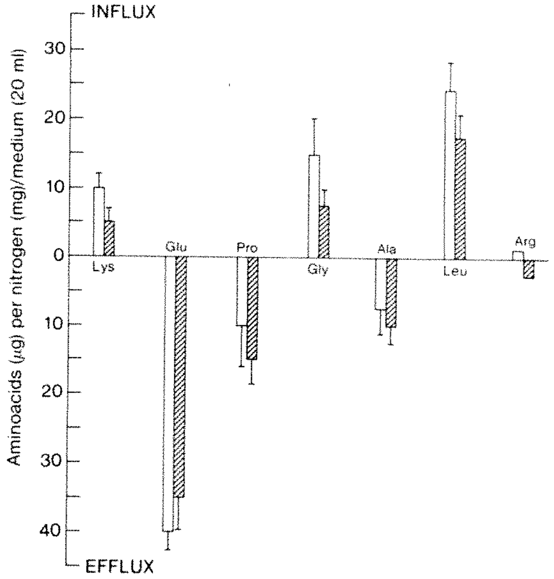

Fig. 3 *Net efflux and influx of amino acids in medium with hydrocortisone (striped bar) and without hydrocortisone (open bar) used to store rabbit cornea. Standard error of mean is shown.*

Glucose. Table 2 shows that in the control medium there was a greater loss of glucose than in the experimental medium ($p<0{\cdot}05$).

Protein. Both the methods of Whitaker and Granum[7] and of Lowry *et al.*[8] were used to determine the protein concentration and showed that the control medium had a greater quantity of protein than the experimental medium (Table 2).

Amino acids. A comparison of the amino acid contents of the different media showed that certain amino acids were more and others were less in the experimental or control medium than that in the

Table 2 *Analysis of MK medium following storage of human and rabbit full-thickness corneal discs, 11 mm in diameter*

	Human cornea			*Rabbit cornea*		
	Medium with steroid *(A)*	*Medium without steroid* *(B)*	*Significance of difference (p)* *(B–A)*	*Medium with steroid* *(A)*	*Medium without steroid* *(B)*	*Significance of difference (p)* *(B–A)*
Glucose µg/ml/disc	22±10	124±40	<0·05	88±20	114±20	<0·05
Protein (Lowry) µg/ml/disc	22·80±6·3	29·78±5·6	<0·01	20·58±3·7	30·60±3·3	<0·05
Protein (UV) µg/ml/disc	42·28±14·2	56·20±20·0	>0·05	38·60±3·6	54·44±7·2	<0·05
pH*	8·2±0·1	8·31±0·1	<0·10	8·30±0·1	8·34±0·1	<0·20
Osmolarity† mmol/kg	331±5·0	338±7·0	<0·10	325±3·0	330±1·0	<0·02

*pH of fresh medium was 7·5±0·2.
†Osmolarity of fresh MK medium was 320±2 mmol/kg.

fresh medium as represented by the line at 0 in the Figs. 1 and 2. Hydrolysis of the medium manifested a greater amount of a given amino acid as compared with its corresponding quantity in unhydrolysed medium (Fig. 1). The net quantity of a given amino acid in the storage medium (control and experimental) was the difference in the values obtained from the hydrolysed and unhydrolysed media (Figs. 2, 3).

Fig. 1 shows the amino acid data for the unhydrolysed and hydrolysed samples of the experimental and control media related to the human cornea. In the unhydrolysed sample the concentrations of leucine and lysine were lower (<20 µg/ml) (Fig. 1A) and in the hydrolysed sample the concentration of glutamic acid was higher (>20 µg/ml) than their respective concentrations in the fresh medium (Fig. 1B).

As shown in Fig. 2, the net quantity of a given amino acid in the medium in which the human cornea was stored (the experimental or control medium) was different from that of the same amino acid in the fresh medium. As compared with the fresh medium, both storage media had (*a*) a greater amount of glutamic acid, alanine, and arginine and (*b*) a lesser amount of leucine, lysine, and glycine. However, the exit from and the entrance into the cornea of most of these amino acids were both influenced in the presence of the steroid. When the steroid was present in the medium, we saw a reduction in the increase of glutamic acid and alanine on the one hand, and a reduction in the decrease of leucine, lysine, and glycine on the other hand (Fig. 2).

Comparing Fig. 3 with Fig. 2 we see that the rabbit cornea also showed a trend similar to that shown by the human cornea. As in the case of human cornea, hydrocortisone decreased the quantity of leucine and lysine in the medium, and also reduced the increase of glutamic acid into the media.

Scanning electron microscopy (SEM) was done on three paired corneas of rabbit—one cornea being stored in the experimental medium and the other in the control medium. The cornea kept in the control medium showed a higher percentage of damaged endothelial cells (Fig. 4A) as compared with the cornea stored in the experimental medium (31% vs 8·2%) (Fig. 4B). When these results were compared with that related to the unstored fresh cornea, the latter hardly showed any damaged endothelial cells (Fig. 4C).

There was no significant difference in the pH between the experimental and control media (Table 2). The osmolarity of the experimental medium tended to be slightly lower than that of the control medium, but the difference was not statistically significant (Table 2).

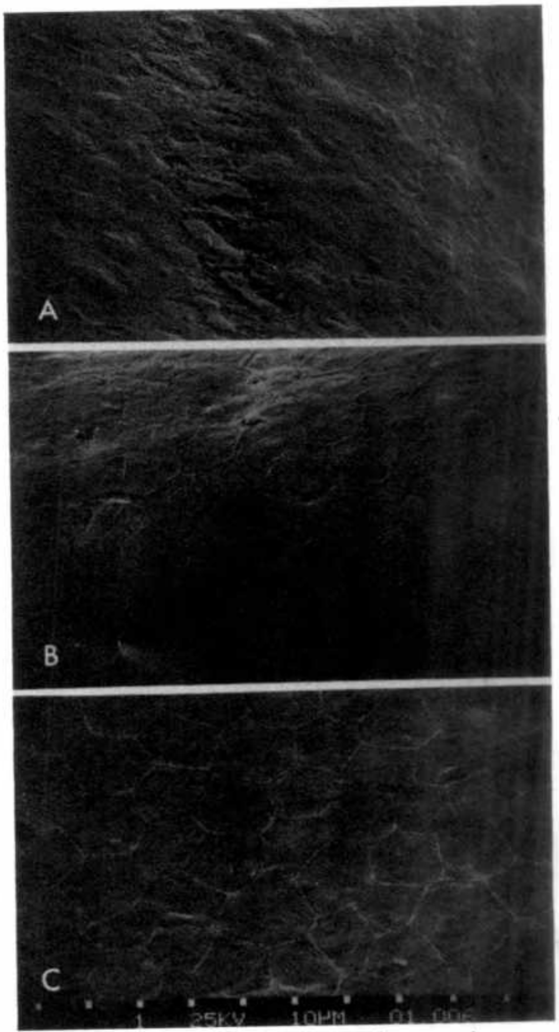

Fig. 4 *Scanning electronmicroscopy of the corneal endothelium.* A: *Cornea stored in the absence of hydrocortisone showing extensive areas of cellular damage.* B: *Cornea stored in the presence of hydrocortisone showing some damaged cells.* C: *Fresh unstored cornea showing undamaged cells.*

Discussion

It has been shown that the corneal endothelial cells from the time of the death of the eye donor undergo rapid structural and functional changes which make them more permeable to organic and inorganic substances.[9] It has also been shown that hydrocortisone (a lysomal membrane stabiliser) by protecting the cell membranes can reduce corneal damage during storage.[4-5] Our present study indicates that the steroid added to the storage medium can influence the entrance into and release of certain specific substances from the cornea.

It is interesting to see that in terms of the water content the cornea stored in the MK medium containing hydrocortisone was more similar to the unstored fresh cornea (compare the p values in Table 1) than to the cornea stored in the medium without the steroid. As the dry weights and the nitrogen contents of the corneas stored in the experimental and control media were identical, the greater weight of the cornea stored in the steroid-free MK medium was obviously due to a greater increase in the entrance of water from the medium into the tissue. Hydrocortisone thus reduced the flow of water into the cornea during storage.

Glucose is required by the donor cornea as early as one hour after the enucleation of the eye.[10] Glucose is one of the major components of the MK medium. Our results showed that both the human and rabbit corneas kept in the steroid-containing medium utilised approximately five times less quantity of glucose than identical corneas stored in medium free of steroid (Table 2). Our glucose results are in agreement with that of Landau,[11] who reported a decrease in the utilisation of glucose by the muscle, adipose tissue, skin, lymphoid tissue, or leucocytes when treated with steroid. Norton and Munck[12] also found a dose related decrease in glucose uptake by macrophage treated with glucocorticoids in vitro.

Our study showed that a greater amount of protein was present in the control MK medium than in the experimental medium. Hydrocortisone thus reduced the release of protein from the stored cornea into the storage medium.

Although we analysed 20 amino acids in our study, we focused our attention particularly on seven of them, known to be abundant in the protein residue of collagen,[13] which is an important constituent of the cornea. In comparison with their respective concentrations in the fresh medium, in both the experimental and control media the concentration of leucine was lower and that of alanine and glutamic acid were higher. Although we do not know the mechanism of the amino acid transfer, the influx of leucine and the efflux of alanine and glutamic acid to and from the stored cornea may be associated with cell membrane damage (Fig. 1). A comparison of the experimental and control media suggests the possibilty of reduction of corneal damage (in terms of amino acids) of stored corneas by steroid (Figs. 2 and 3). An analysis of the net difference between the influx and efflux values of the different amino acids shows that the entrance of leucine into the cornea and release of glutamic acid from the cornea were quite remarkable (Figs. 2 and 3). As steroid tended to reduce both the entry and exit of these two amino acids to and from the stored cornea, we feel that a study of these amino acids could possibly be utilised in judging the quality of a stored cornea in tissue culture medium.

The human donor eyes, from which the corneas were obtained, varied in terms of the period between death and enucleation, cause of death, donor age, etc. In contrast, the eyes of rabbits were obtained immediately after their death. In view of our previous work[2] we would assume that when we received the human eyes they had a greater degree of corneal autolysis as compared with the rabbit eyes. It was, therefore, interesting to note that the fresh rabbit corneas and the stored human corneas behaved in a similar fashion with respect to the qualitative pattern of exit from or entrance into the corneas of the amino acids mentioned before. Quantitatively, however, both the experimental and control media related to the rabbit corneas had lower concentrations of leucine and lysine as compared with the experimental and control media related to the human cornea. We believe that the above quantitative difference between the rabbit and human corneas, apart from the species difference, was due to the difference in the degree of autolysis present in the two types of corneas when we started the experiments. However, at present we cannot explain why some of the amino acids were affected in one way and the others in another way.

With regard to the uptake of leucine by the cornea from the storage media, the work of Hanna[14] seems to be interesting. He reported that corneal cells can absorb leucine and incorporate it into new protein. Scott and Friedenthal[15] showed that leucine uptake is stimulated by lactate. Since lactate is known to be produced during mid-term storage of the cornea,[16] it is possible that to form new proteins leucine is utilised by the surviving cells in the autolysing stored cornea. In one of our studies (unpublished data) we have seen a gradual increase in the uptake of radioactive leucine from the MK medium (without steroid) into the cornea with the progress of the storage time. In our present study we have seen that hydrocortisone reduced the entrance of leucine from the medium to the cornea. This may be due to a reduced demand for the production of new proteins[14] in a more favourably stored cornea as a result of the reduction of tissue autolysis by steroid.

The entrance and exit of the amino acids into and from the stored cornea were probably related to the damage of the corneal cell barriers. A comparison of the results of our present SEM study on the corneal endothelium of fresh unstored rabbit eyes with the results of our previous SEM study on the corneal endothelium of stored human eyes[2] showed that the amount of cell damage in the stored human cornea was greater than that in the fresh rabbit cornea. Both our present (Fig. 4) and previous studies[2] also showed that steroid can reduce structural damage of the corneal endothelial cells from both species.

We did not detect any significant difference in the pH values among experimental, control, and fresh media. Hull *et al.*[17] also did not find any significant alteration of pH in the medium in which corneas were stored up to seven days, but they found some change after 21 days.

Otori[18] showed that the electrolyte content of the cornea decreased when the whole eye was stored in the moist chamber. Hull *et al.*[17] found a decrease in the potassium content of the cornea stored in the MK medium for seven days. The decrease of the electrolyte content of the stored cornea would tend to increase the electrolyte concentration of the storage medium and thus could be a guide for determining the degree of tissue damage.[19] In our present study we were unable to detect any statistically significant change of osmolarity of the storage media. However, as shown in Table 2, we noticed a trend towards the reduction of the electrolyte concentration (mmol) of the storage medium when steroid was added to it.

In conclusion, we think that the use of steroid in the storage medium should be beneficial in preventing corneal damage during mid-term and possibly long-term storage of the donor cornea. Further, we believe that a chronological biochemical analysis of the MK medium particularly for the increase of protein and glutamic acid and the decrease of leucine and glucose could be helpful in monitoring the nature and rate of damage to the cornea stored in tissue culture media.

This work was supported by grants from the Medical Research Council of Canada, the Canadian National Institute for the Blind out of the E A Baker Foundation for the Prevention of Blindness, Independent Order of Odd Fellows and Rebekahs of Ontario, and the Lions International District A-16 Ophthalmological Research Foundation, Canada.

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Correspondence

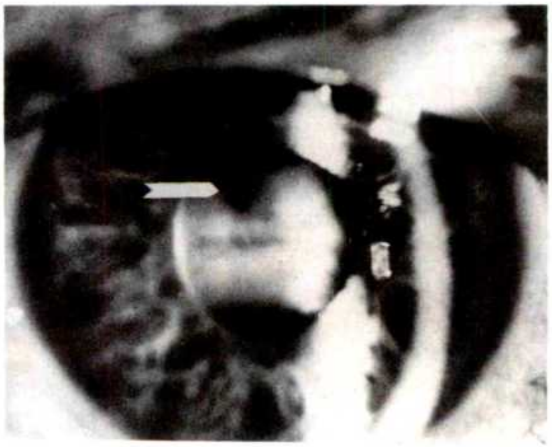
Intralenticular haemorrhage complicating pulsed laser iridotomy

SIR, The pulsed laser has recently been described as a 'non-surgical' means of producing a peripheral iridotomy. The complications of this procedure have been reviewed[1] and include iritis, pigment dispersion, haemorrhage, transient elevation of intraocular pressure, corneal or lens damage, lack of patency of the iridotomy, and blurring of vision. We report a case in which Q-switched neodymium (Nd)-YAG iridotomy was complicated by intralenticular haemorrhage.

Case report

A 69-year-old female patient underwent a left trabeculectomy for primary open angle glaucoma which had not responded to conventional medical treatment. Postoperatively it was noted that the pigment layer of the iris remained intact, and pulsed laser treatment was considered necessary to complete the iridectomy.

A Biophysic Médical Q-switched Nd-YAG laser was used in its fundamental mode at an 18° convergence angle. Ten lesions were applied at 2 mJ in the mid portion of the iridotomy, aiming at the pigment layer on each occasion. Each shot produced a minute hole. Persistent bleeding had been a problem during surgery and had resulted in a 1·5 mm hyphaema. The iridotomy was also complicated by haemorrhage. However, tests of blood clotting were all within the normal range. Following this procedure it was noticed that intralenticular haemorrhage had taken place (Figure). This had remained unchanged in character for two months, and the current visual acuities are 6/9 (corrected) left and right.



We presume that the laser pulses resulted in microscopic rupture of the lens capsule which has subsequently sealed spontaneously. The haemorrhage within the lens is discrete, lamellar, and lies deep to clear cortical lens material. This appearance would suggest that blood entered the lens by a capillary effect while there was a breach in the capsule and flowed between the lamellae of the lens cortex.

This complication could have been avoided by applying the laser treatment more peripherally. This case highlights the fact that the lesions produced by a pulsed laser are not discrete and that underlying tissues can be damaged. We believe that this is the first reported case of discrete intralenticular haemorrhage caused by Q-switched Nd-YAG laser treatment.

DONALD M I MONTGOMERY
GORDON N DUTTON
Tennent Institute of Opthalmology,
Western Infirmary,
Glasgow G11 6NT

Reference

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Notes

Orthoptic congress

The Sixth International Orthoptic Congress and Trade Exhibition will take place at Harrogate on 29 June–4 July. It will be opened by Princess Anne. Details from Mrs J Clayton, Chairman of Organising Committee, British Orthoptic Society, Tavistock House North, Tavistock Square, London WC1H 9HX.

Hoyt chair

Fellows, students, colleagues, and friends of Dr William F Hoyt are in the process of establishing an endowed chair in neuro-ophthalmology at the University of California, San Francisco, in his name. The chair will recognise Dr Hoyt's many contributions to the field of neuro-ophthalmology, including teaching, research, and clinical observations. People interested in obtaining further information regarding the chair should contact either Creig Hoyt, MD, at 400 Parnassus Avenue, Suite 704, San Francisco, California 94143, USA, or Neil R Miller, MD, Johns Hopkins Hospital, 600 North Wolfe Street, Wilmer Eye Institute, Maumenee Building B-107, Baltimore, Maryland 21205, USA.

Canadian Ophthalmological Society

The 50th Anniversary Meeting of the COS will be held on 20–23 June at the Queen Elizabeth Hotel, Montreal. Details from J Paul Le Bel, COS Executive Director, Ottawa, Ontario, or Cathy Hanson, Berger & Associates Canada Inc., Toronto, Ontario, Canada.

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